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Behavioral and Neural Loss Aversion in Major Depressive Disorder: A Neuroeconomic Model of Depression

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Abstract

Background: Major Depressive Disorder (MDD) is a significant public health issue. Previous research on the pathophysiology of depression in adults has demonstrated abnormal neural processing associated with depression symptomatology including alterations in reward and aversion circuits. Loss aversion (LA), or the concept that individuals evaluate outcomes based on losses and gains and are more sensitive to losses than to gains, provides targets to identify neural correlates of the abnormal processing of losses and rewards among depressed patients. Thus far, behavioral and neurological characterizations of LA in depressed patients are poorly understood.

Methodology/Principal Findings: Data for this project was derived from a large-scale project completed at Harvard Medical School/Massachusetts General Hospital. In the current study, we used model-based functional magnetic resonance imaging (fMRI) to investigate differences between patients with MDD and matched healthy controls with regard to: 1) behavioral LA, 2) brain activation to LA, and 3) the relationship between behavioral LA and neurological LA (i.e., neural differential sensitivity). Within a sample of 45 healthy controls and 29 patients with MDD, we found that a subset of individuals in each group exhibited atypical patterns of LA. More specifically, they consistently rated either positive values as negative or negative values as positive. Among those subjects with typical LA (n=32 controls and n=20 patients), healthy individuals trended towards higher evaluation of potential rewards than patients with MDD. While both healthy controls and depressed patients showed similar patterns of neural activation relative to subjective ratings of losses and gains, the healthy control group demonstrated neural activation in more regions than patients with MDD. Of the *a priori* regions examined (i.e., Nucleus Accumbens, (NAc), Ventral Tegmentum/Substantia Nigra (SN/VTA), and

Amygdala), only the NAc and SN/VTA were involved in the relative evaluation of potential losses and gains, but these effects differed between groups. Controls demonstrated decreased activation in the R NAc to both positive and negative stimuli whereas the depressed group demonstrated decreased activation in the R and L NAc to only negative stimuli. Further, only healthy controls demonstrated increased activation to potential losses in the SN/VTA. Finally, association between behavioral LA and neural sensitivity was observed among controls only in the right orbitofrontal cortex (OFC) for the healthy control group but not individuals with MDD.

Conclusion/Significance: These results raise the possibility that individuals with MDD, compared to healthy controls, may have a disruption in a reward/ aversion neural network. Specifically, in patients with MDD, disruptions in this network appear to manifest as decreased activation in the SN/VTA in response to negative stimuli and lack of involvement of the NAc in response to positive stimuli. Behaviorally, this may manifest as a decreased positive appraisal of potential gains in depressed patients relative to controls. Results also suggested that while behavioral and neural LA are correlated in the healthy controls in the right OFC, patients with MDD show a different pattern of interactions within the reward circuitry. This study highlights that depression may be understood using neuroeconomic models of behavior, including LA, to elucidate disrupted relationships between behaviors and neural processing of rewarding and aversive stimuli in patients with MDD. This may lead to the identification of biological substrates of depression symptomatology that can be targeted through behavioral and pharmacological interventions.

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Dedication

This dissertation is dedicated to my amazing family who has supported me throughout this journey. Thank you to my parents, Barb and Tom, my siblings and sibling-in-law, Amy, Andy, and Lauren, and to my niece and nephews, Emily, Henry, Thomas, and Aidan for all of your support and love. I especially thank my loving husband, Josh, and my amazing daughter, Josephine ("Effie"), who keep me smiling and loving life every single day.

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Review of Relevant Literature

Major Depressive Disorder (MDD) is an important public health issue. Each year, approximately 16 million adults in the United States experience a depressive episode (Substance Abuse and Mental Health Services Administration, 2013). People with MDD have an increased risk of early death, in part due to an increased risk of suicide (Bostwick & Pankratz, 2000). Depression has also been associated with the "onset, persistence, and severity" of physical illnesses (Kessler & Bromet, 2013) and is highly comorbid with other psychiatric conditions including substance use disorders (Swendsen & Merikangas, 2000). With so many afflicted, the economic costs are staggering. Individuals diagnosed with MDD pay significantly more in non-mental health care costs compared to those who without a diagnosis of MDD (Welch, Czerwinski, Ghimire, & Bertsimas, 2009). The cost of MDD also impacts the US economy at large, resulting in decreased revenue of approximately $44 billion per year due to the loss of productivity time. This is $31 billion more than losses in productivity attributed to employees without depression (Stewart, Ricci, Chee, Hahn, & Morganstein, 2003). Due to the need for early detection and effective intervention, studies utilizing neural-behavioral integration are important for understanding the underlying neural mechanisms associated with depressive symptoms to more effectively intervene upon them (Davidson et al., 2002).

An important predictor and concomitant of MDD is dysfunctional information processing, with a bias towards negatively-valenced information (Roiser, Elliott, & Sahakian, 2012; Yang, Zhang, & Yao, 2014). This bias in patients with MDD can be understood within the context of a continuum of valence, or degree of attractiveness

Merriam-Webster, 2017). On one extreme is positive valence, or reward, which is generally understood as positive stimuli that would elicit approach or positive anticipation. On the other extreme is negative valence, or aversion, that elicits avoidance or negative anticipation. Patients with MDD exhibit a decreased responsiveness to reward (Henriques & Davidson, 2000), and decreased reward seeking has been identified as a possible risk endophenotype for the disorder (Mannie, Williams, Browning, & Cowen, 2015). Depressed patients also show higher levels of risk aversion compared to controls (Smoski et al., 2008) but similar to the performance of other populations who exhibit increased harm avoidance, including those with increased anxiety (Schmitt, Brinkley, & Newman, 1999).

The pathophysiology of depression in adults has been heavily researched, and specific forms of abnormal neural processing have been associated with depressive symptomatology. Much of this dysfunction centers on brain circuitry between the cortex and the limbic system. Specifically, alterations in reward and aversion circuits which process emotional stimuli are seen as important biological substrates for depression (Blood et al., 2010; Pizzagalli et al., 2009; Zhang, Chang, Guo, Zhang, & Wang, 2013). The amygdala likely plays a role in detecting, interpreting, and perpetuating emotional reaction to a stimulus (Disner, Beevers, Haigh, & Beck, 2011). Individuals with MDD show increased intensity and duration of amygdala activation to emotional stimuli compared to healthy controls (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). Structural and functional changes in the amygdala have been linked to biases towards negative information in individuals with depression, although the direction of change has conflicting results (Hulvershorn, Cullen, & Anand, 2011). Amygdala activation is likely

regulated by higher cortical areas, such as the DLPFC. However, patients with recurrent MDD have been shown to have decreased gray matter volume (Li et al., 2010) and decreased reactivity DLPFC to both negative and positive stimuli (Gotlib & Hamilton, 2008). This suggests an impaired ability of the DLPFC to regulate amygdala reactivity in patients with MDD.

Another region implicated in depression symptomatology is the nucleus accumbens (NAc). Along with the anterior cingulate cortex (ACC), altered responses to rewards in the NAc has been linked to anhedonia (i.e., the reduced ability to experience pleasure) in depressed patients (Wacker, Dillon, & Pizzagalli, 2009). Research has also shown that the NAc and caudate show decreased activation in response to rewards and reward cues in depressed individuals (Pizzagalli et al., 2009), which is consistent with studies utilizing diffusion tensor imaging (DTI) that have shown altered structural connectivity in the frontal-thalamo-caudate regions in MDD (Korgaonkar, Fornito, Williams, & Grieve, 2014). The NAc and prefrontal cortex (PFC) also decrease more dramatically following positive stimuli (Pizzagalli et al., 2009). Post-mortem studies of individuals with MDD also reveal histopathological abnormalities in the NAc, orbital cortex, and ACC (Price & Drevets, 2012).

The NAc is part of the mesolimbic reward circuit that contains multiple regions deemed critical to the processing of rewards, including the ventral tegmentum area (VTA) (Nestler & Carlezon Jr, 2006). The mesolimbic dopamine reward circuit involves complicated circuitry that includes both the excitation and inhibition of dopamine neuronal activity in response to aversive cues (Lammel, Lim, & Malenka, 2014). Rodent models with manipulations of proteins within this circuit exhibit behavioral phenotypes

relevant to depression (Nestler & Carlezon Jr, 2006). Research has also found individuals with MDD exhibit an increased response of the insula and reduced response of the caudate during anticipation of a monetary reward (Zhang et al., 2013). Other regions implicated in depression include the hypothalamus (Hulvershorn et al., 2011; Price & Drevets, 2012) and orbitofrontal cortex (OFC) (Drevets, 2007).

Prospect Theory

Taken together, these findings raise the possibility that depression may stem from an abnormality in the relative processing of gains and losses – namely, individuals with depression have increased sensitivity to losses relative to gains. Thus, their bias towards negative information may be associated with increased loss aversion (LA), or the tendency of individuals to be more sensitive to losses than to gains when evaluating outcomes (Kahneman & Tversky, 1979) (See Figure 1). LA is one of many measures that can be derived from reward/aversion valuation curves. LA is calculated using two components: The curve that indicates a person's level of approach (slope = s+) and the curve that indicates a person's level of avoidance (slope = s-). LA has traditionally been measured with paradigms based on Prospect Theory involving monetary loss. Prospect Theory states that individuals make decisions based on the potential value of losses and gains rather than the final outcome (Kahneman & Tversky, 1979) and uses probability weighting function computation to translate objective information into subjective estimates (Pammi et al., 2015).

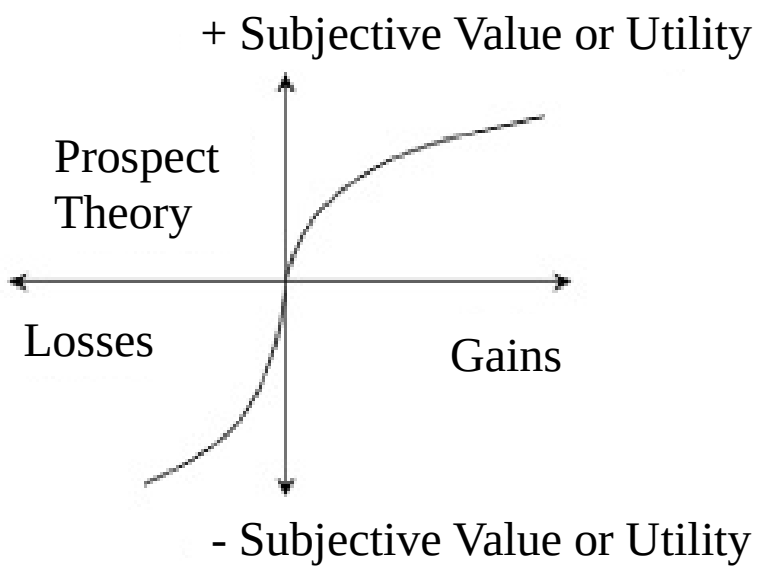

Figure 1. This graphs shows the function of subjective value versus actual loss and gains. According to prospect theory, the steeper slope close to the original for the evaluation of losses demonstrates that individuals are more sensitive to losses than to gains. This figure was used with permission (Lee et al., 2015).

Prospect Theory is just one conceptualization of reward, but alternative theories exist with different ways of calibrating value and therefore reward. In a basic "stimulus-response" model, rewards are goal-objects of stimuli that produce repeated approach or response behaviors. For example, a mouse will repeatedly press a bar to receive cheese, and therefore the cheese is the reward. This reward can explain both the intensity and direction of the behavior, specifically, if the reward is particularly salient to the mouse, he will pursue behaviors that will lead to more cheese by pushing the bar more intensely (Breiter et al., 1997; Breiter, Gasic, & Makris, 2006; Breiter & Rosen, 1999; Breiter & Gasic, 2004). In Prospect Theory, reward is a calibration based on individual liking/wanting against what a group or market likes/wants (Breiter, 2012; Kahneman & Tversky, 1979; Lee et al., 2015). Alternatively, in the Matching Law, reward is a calibration of wanting related to a reinforcer, or goal-directed object in the environment, and can be measured by the relative rates of enforcement between objects (Reed &

Kaplan, 2011). In the Hedonic Deficit Theory (i.e., Alliesthesia), reward represents the calibration of wanting in relation to a deficit of a physiological output, for example, feeling gastric contractions when hungry even though these contractions are not otherwise felt (Cabanac, 1971). Lastly, Relative Preference Theory (RPT) postulates that reward represents a calibration of individual wanting based on memories of outcomes from previous behaviors that were focused on goal-objects (Breiter & Kim, 2008; Kim et al., 2010; Lee et al., 2015; Livengood et al., 2017; Viswanathan et al., 2017).

Broadly speaking, LA is the tendency of individuals to overvalue losses compared to gains. LA, however, may be defined and measured in different ways. Global definitions of LA measure LA across the entire value function. In Prospect Theory, the slope of the negative value/utility function (s-) is compared to the slope of the positive value/utility function (s+) to obtain an absolute value of s-/s+ (Lee et al., 2015; Livengood et al., 2017; Viswanathan et al., 2017), therefore framing loss and gain with respect to a neutral point (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001). This slope represents the value of LA. Prior research suggests that individuals rate potential losses with approximately twice (2.25x) the weight as potential gains (Tversky & Kahneman, 1992). Paradigms approximating LA can be measured by monetary tasks which attend to differences in how individuals process relative losses and gains. If the graphs for gains and losses are compared over their range, this is considered a "global" measure of LA; whereas if they are evaluated close to the origin (as initially defined by Kahneman and Tversky, 1979), then they make a "local" measure of LA. For example, in one PT paradigm, participants are shown two spinners, each of which can result in a gain of $10 or a loss of $8. One spinner has a higher likelihood of gain ("good spinner") while the

other has a higher likelihood of loss ("bad spinner") (Breiter et al., 2001). Participants rate how they feel about the spinner as it spins, and then again when the spinner has stopped and they have won or lost money. Participants expectations based on probabilities can then be extracted to produce a "global" measure of LA, as well as how these expectations affect the perception of the outcome [a counterfactual comparison, (Breiter et al., 2001)]. In another task of global LA, participants were presented with 50/50 monetary gambles that represented a 50% chance of winning and 50% of losing (e.g., presentation of +$12 and -$14). In this forced choice paradigm, participants were required to choose whether or not to accept the gamble, the consequence would affect their overall total (Tom, Fox, Trepel, & Poldrack, 2007).

Alternatively, LA can be defined by a "local" definition and is measured close to the inflection point of the value/utility function (Lee et al., 2015). For example, in RPT, data is derived from key press tasks of preference-based decision-making. RPT does not make parametric assumptions. Rather, it uses an entropy variable as a measure of uncertainty with making a choice (Kim et al., 2010; Lee et al., 2015; Livengood et al., 2017; Viswanathan et al., 2017). By using a keypress to calibrate reward value of based on individual preference, RPT can be measured using nonmonetary stimuli and thus broaden the generalizability of the findings (Lee et al., 2015). They also allow one to separate LA from other components, such as utility curvature. RPT, thus, allows both individual and group characteristics to examined in a lawful way (Breiter et al., 2015; Kim et al., 2010). The differences in measuring LA, whether global or local, as well as differences in PT tasks, are important to consider in as much as different measurements of LA will reflect differences in the cognitive processing of a stimuli (Lee et al., 2015). In

this study, we chose to use a Monetary Game of Chance derived from Prospect Theory (Breiter et al., 2001). This allowed us to measure LA during the phase of cognitive processing when participants were shown their probability of winning or losing, thus allowing us to extract perceptions of potential loss or gain while anticipating an outcome.

Previous neuroimaging studies of LA in nondepressed individuals has pointed to the importance of the amygdala, NAc, and VTA, as well as the orbital cortex, caudate, putamen, and thalamus in reward processing (Breiter et al., 2001; Canessa et al., 2013; Tom et al., 2007; Viswanathan et al., 2015). Patients with amygdala lesions showed greatly reduced LA compared to controls (De Martino, Camerer, & Adolphs, 2010). Studies have also begun to use the activation of certain brain regions relative to losses and gains as a proxy for neural LA to better understand if these patterns of LA neural sensitivity correlate with behavioral LA. This is known as Neural Differential Sensitivity (NDS), which was first developed by Tom and colleagues (2007). NDS is defined as the difference between activation to aversive stimuli (negative s-) and the level of activation to rewarding stimuli (negative s+) within a single brain region. NDS can be correlated with behavioral LA to provide a direct comparison of the differences in aversion and reward processing between behavioral and neurological measures (Tom et al., 2007; Viswanathan et al., 2015). In a decision-making task, healthy adults showed neural LA in the ventral striatum and prefrontal cortex, and this predicted behavioral LA (Tom et al., 2007). Another study utilizing approach/avoidance to affective faces (i.e., faces displaying angry, fearful, happy, sad, or neutral expressions) found correlations between NDS in the VTA and NAc and behavioral LA related to aging (Viswanathan et al., 2015). Specifically, this study found that while there was no relationship between age and LA,

NDS increased in the NAc with increasing age, suggesting neural efficiency of processing relative losses and gains decreases with age. This highlights that NDS may be critical in understand differences in reward/aversion processing that is not apparent through simply examining behavioral LA. The value of LA research is heightened by research showing that behavioral LA can be changed. Specifically, utilizing emotion regulation strategies (similar to those used in the treatment of MDD) while making financial decisions can reduce behavioral LA (Sokol-Hessner et al., 2009). Moreover, this reduction has been found to be correlation with a reduction in amygdala activation in response to loss (Sokol-Hessner, Camerer, & Phelps, 2012).

Prospect Theory provides a unique framework for understanding the abnormal processing of losses and gains in depressed patients compared to controls. Researchers are utilizing LA to better understand other psychiatric illnesses with symptoms that reflect an abnormal evaluation of rewards relative to loses, including schizophrenia (Currie et al., 2017; Trémeau et al., 2008), gambling disorder (Quester & Romanczuk-Seiferth, 2015), and substance abuse (Chivers & Higgins, 2012), as well as induced anxiety within a non-psychiatric population (Charpentier, Hindocha, Roiser, & Robinson, 2016). Researchers are also beginning to see the value of utilizing prospect theory to better understand depression symptomatology. In a game of chance based on prospect theory (Breiter et al., 2001), patients with MDD demonstrated microstructural abnormalities in the substantia nigra and ventral tegmentum area (SN/VTA). Moreover, they also found an abnormal overall behavioral pattern of responding compared to controls while anticipating potential monetary losses and gains (Blood et al., 2010). One study employed a decision-based gambling task to examine NDS in patients with MDD.

Results showed similar regions were implicated in neural LA for both MDD and controls, including the amygdala, VTA, DLPFC, insula, and ACC. This suggested that although similar networks were used by both MDD and controls, brain-behavior correlation of LA between groups highlighted potential differences in differential activation (Pammi et al., 2015). However, little is known about how neural LA derived from the anticipation of losses and gains differs between depressed and non-depressed individuals.

Significance and Purpose of the Study

The possibility exists that regions implicated in depressive symptomatology overlap with those showing differences in LA behavior. With this in mind, the overall aim of this study is to examine whether differences in both behavioral and neural LA are apparent in individuals with and without MDD. We expect to see a relationship between behavioral and neural processing of LA in healthy individuals that is not present in depressed individuals. By using a model-based fMRI approach, we hope to provide a unique perspective on the neurological basis of depression symptomatology that can inform new and more efficacious therapeutic targets for depression.

Statement of Hypotheses

Aim 1 was to assess behavioral LA differences between individuals with and without MDD during a task in which they are asked to anticipate rewards and losses. We expected the MDD group to exhibit greater LA, that is, to be more loss averse, and to undervalue potential gains compared to controls.

Aim 2 was to assess for differences between individuals with and without MDD in neural activation during the anticipation phase of an fMRI task of LA. We used a

model-based approach to allow us to evaluate how patterns of neural activation were specifically matched to the relative weighting of losses and gains for each individual. Based on previous research, we expected similar neural networks to be involved for both individuals with and without MDD. We also expected different relative levels of hyper- and hypo-activation within these regions. For this analysis, we examined three primary *a priori* regions: SN/VTA, amygdala, and NAc, along with six secondary *a priori* regions: DLPFC, insula, OFC, caudate, ACC, and hypothalamus. We hypothesized that healthy controls would show greater activation in regions associated with higher order processing (such as the OFC and DLPFC) whereas those with MDD would have more activation in subcortical regions (e.g., SN/VTA, NAc, and amygdala).

Aim 3 was to better understand the relationship between behavioral LA and neural LA in both groups. To do this, we examined the correlations, or lack thereof, between behavioral LA and a measure of neural differential sensitivity (NDS) based on the differences in neural activation between positive and negative stimuli. We expected the healthy control group would show a clear relationship between areas involved in reward neural circuitry and behavioral LA, but that this relationship would not exist in the MDD group.

Participants

Data for this study were derived from the Massachusetts General Hospital (MGH) Phenotype Genotype Project in Addiction and Depression (PGP). All subjects were recruited via advertisements. Subjects were thoroughly screened and excluded from the study if they were suicidal or at risk for suicide, pregnant, or severely respiratory compromised or if they had uncontrolled hypothyroidism or hyperthyroidism, a history of a head trauma with neurological sequelae, diabetes or abnormal hemoglobin A1C, a serious medical condition, a seizure disorder, or a history of delirium, dementia, or other mental disorder due to a general medical condition. Participants were also excluded if it was deemed ineligible to have an MRI either due to having a medical device incompatible with MRI, claustrophobia, or body weight index that would make the MRI infeasible. Women were scanned during their mid-follicular phase as confirmed by hormonal testing.

Additionally, participants in the MDD Group met criteria for MDD based on a physician-administered structured interview (SCID I/P; First, Gibbon, Spitzer, & Williams, 1996). They were excluded if they met criteria for a current diagnosis or lifetime history of primary psychotic disorder, bipolar disorder, eating disorder, substance abuse disorder, generalized anxiety disorder, panic disorder, PTSD, or OCD as determined by the SCID. Participants in the healthy control group were only included if they did not meet criteria for any Axis I psychiatric disorder as determined by the SCID.

Our two groups (depressed - MDD and healthy controls - CON) were matched on 5 variables: gender, age, race, years of education, and handedness. Subjects were also

chosen on the basis of having complete and valid data for both the behavioral and imaging portions for the Monetary Game of Chance (see fMRI paradigm below). Our sample included 45 CON and 29 MDD participants. Each subject's ratings were evaluated based on their condition-wise mean values across the entire anticipation/outcome epoch to determine whether they exhibited typical LA. Typical LA was defined as a bivalent value function in which positive ratings were given when presented with a higher likelihood of gains (i.e., Good Disk) and negative ratings were given when presented with a higher likelihood of losses (i.e., Bad Disk). This resulted in the identification of eight subjects who had negative ratings of potential gains (i.e., univalent in the negative direction), fourteen subjects with positive ratings of potential losses (i.e., univalent in the positive direction), and one subject who fell in both of these categories (i.e., bivalent in the opposite direction than was expected). These unusual rating patterns resulted in negative slopes that were not compatible with the neuroimaging analyses. Therefore, behavioral analyses were conducted with the full cohort (hereby called MDD-FC and CON-FC) while the neuroimaging analyses were conducted with participants demonstrating typical LA (i.e., univalent towards positive or negative and bivalent in opposite direction than expected were removed). The subjects with typical LA (hereby called CON-TLA and MDD-TLA) were again matched on the basis of the five variables listed above, resulting in a final cohort of 32 CON-TLA and 20 MDD-TLA.

Measures

Edinburgh Handedness (Oldfield, 1971) A questionnaire to assess for hand dominance of the individual.

Hamilton Rating Scale-Depression *(HAM-D; Hamilton, 1967)* The HAM-D is a 31-item clinician-rated scale of depression severity and demonstrated sufficient reliability and validity (Cusin, Yang, Yeung, & Fava, 2010).

Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID I/P; First et al., 1996) is a semi-structured interview designed to make diagnoses according to DSM IV (American Psychiatric Association, 1994) with moderate to excellent interrater reliability (Lobbestael, Leurgans, & Arntz, 2011).

Procedures

fMRI paradigm - *Monetary Game of Chance*

Subjects completed three practice sessions of the task outside of the scanner. While in the MRI scanner, participants were presented with two spinners with different sectors, one representing gain (+$10) and the other representing loss (-$8). One spinner is considered the "good" spinner because the green sector labeled with +$10 has two-thirds odds (as indicated by its proportion of the circular spinner) while the red sector labeled -$8 has one-third odds. The second spinner is the "bad" spinner and has the red sector (-$8) with two-thirds odds and the green sector (+$10) with one-third odds. The spinner has two phases: (i) the prospect phase, when the subject is presented with the spinner, and (ii) the outcome phase, in which the subject learns how much he/she has won or lost. During the first 0.5 seconds of the prospective phase the display is static. Next, an arrow appears and spins around the center of the spinner for 9.5 seconds. During this time, the subject is asked to rate his/her anticipatory subjective feeling about the spinner on a scale from -10 to 10, with -10 being the maximum negative feeling and 10 being the maximum positive feeling (Lee et al., 2015).

After the prospect phase, the spinner stops on either the red or the green sector and indicates a loss or gain. During this time, the arrow flashes where it has landed and the subject is asked to make a rating about his/her subjective feeling about the outcome of the spinner on the same -10 to 10 scale. For the last 0.5 seconds, a black disk is projected as a mask. Fixation trials are presented between spinner trials. During the fixation trial, an asterisk appears for 19.5 second in the center of the display followed by a 0.5 second black mask. Trial sequence is pseudorandom and counterbalanced so that each type of trial (e.g., “good disk loss,” “bad disk loss”) is proceeded and followed the same number of times by all four spinner/outcome combinations across two runs (Lee et al., 2015) (see Figure 2).

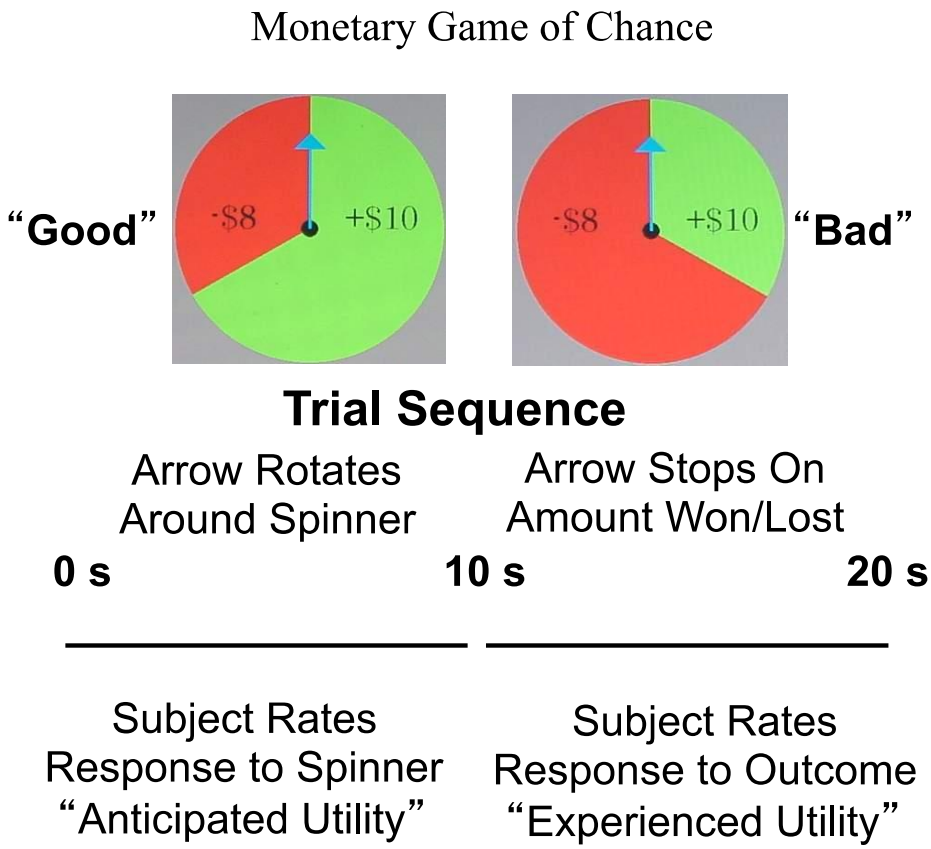

Figure 2. While in the scanner, participants were presented with a "Good" spinner (on left) or "Bad" spinner (on right) and asked to rate their subjective feelings about the outcome of the spinner on a scale from -10 to 10 (10 being most positive) before the spinner stopped spinning. Participants were asked to then rate their subjective feelings of the outcome using the same scale. Reprinted with permission from the authors of Lee et al., 2015.

Image acquisition.

Imaging data was collected using a Siemens 3.0 Tesla Sonata Magnet System (Siemens AG, Medical Solutions, Erlangen, Germany) and an eight-channel phased-array receive-only RF coil. BOLD functional images were acquired using gradient-echo EPI (TR = 2.5 sec; TE = 30msec; $\alpha = 90°$; 3.125 mm x 3.125 mm x 3 mm resolution), with slices aligned parallel to the AC–PC line and to the inside curve of the FOC to minimize signal distortion in this region (Deichmann, Gottfried, Hutton, & Turner, 2003; Gasic et

al., 2009). Structural images were acquired using a high resolution T1- weighted MPRAGE sequence with 192 sagittal slices over the full head volume (matrix = 224 x 256, FOV = 224 x 256 mm^2; thickness = 1 mm, no gap) (Gasic et al., 2009).

Rationale for Statistical Analyses

Comparing sociodemographic and clinical variables.

Control and MDD groups were matched on demographic variables to better characterize group membership. ANOVAs were used to compare the continuous variables (i.e., age, years of education). Pearson's Chi-squared were used to compare categorical variables (i.e., race, gender, handedness). Data on depression severity in the MDD group, as measured by the HAM-D, was also compiled.

Comparison of behavioral loss aversion.

Actuarial values were calculated based on the expected utility (i.e. expected reward) of the spinner based on the probabilities displayed on the disk. More specifically, the good disk has 2/3 chance of winning $10 and 1/3 chance of losing $8. The expected utility is (2/3)*10 + (1/3)*-8 = 4. Conversely, the bad disk has a 2/3 chance of losing $8 and a 1/3 chance of winning $10. Therefore, the expected utility is (2/3)*-8 + (1/3)*10 = -2. These expected utilities make up the values on the x-axis of the value function. The y-axis is the subjective value (i.e. the subjects' average rating of the good spinner or the bad spinner). The slope of the value function to the left side of the inflection point is s-, meant to represent losses or avoidance. The slope of the value function to the right of the inflection point is s+, meant to represent gains or approach. LA is calculated as the absolute value of the ratio of these slopes (s-/s+).

A Shapiro-Wilk's test was used to assess whether the three LA variables (s-, s+, and LA ratio) were normally distributed within each group. If outliers were detected, a Grubb's Test (Grubbs, 1950) determined whether or not these values were considered outliers. If distributions were not normal following the elimination of outliers, nonparametric tests (i.e., Mann-Whitney) were used to assess Aim 1 and determine differences in behavioral LA between groups. A Bonferroni correction was applied to control for multiple comparisons (.05/3 = .017).

fMRI analysis.

All MRI data was stripped of epidermis, skull, intracranial pia, arachnoid, and dural layers. fMRI data underwent further preprocessing. Voxel misalignment was detected using the AFNI motion correction module. Participants were excluded if after two passes of AFNI's motion correction, the mean displacement on any frame (x,y,z) was greater than 1.5 mm or the angle displacement was greater than 1 degree in any direction. Motion correction was conducted using MCFLIRT in FSL. FSL FEAT was used to run spatial smoothing using a 3D kernel (FWHM = $5mm^3$). A temporal smoothing was implemented using a high pass filter with a 90 second cutoff.

To address Aim 2, we utilized model-based fMRI, meaning that subjects' behavioral data is incorporated into the computational model "to find specific values for the free parameters in the model" (O'Doherty, Hampton, & Kim, 2007). Unlike task-based fMRI that can discover what brain region is involved in the completion of a task, model-based fMRI allows researchers to constrain the parameters of the model so that inferences can be made about which regions are involved in specific functions. For our study, each image series was fitted to a linear signal model using each subjects'

functional time series data relative to fixation. Regressors were assigned based on the behavioral responses of each individual during the anticipation phase of the Monetary Game of Chance. Although regressors are typically denoted with a value of "1", in this analysis, regressors were assigned an actuarial slope value used in the ratio of LA (s+ or s-, see "Comparison of Behavioral Loss Aversion" section above). This provided a proxy for LA through separate analyses of a subject's approach to good stimuli (i.e., Good Disk presentation) and a subject's avoidance of bad stimuli (i.e., Bad Disk presentation). For example, in the first analysis, to assess increased activation to positive stimuli relative to the behavioral rating, the individual subject's actuarial value of s+ was used instead of "1" to designate a good disk presentation. Conversely, in a separate analysis, to assess decreased activation to positive stimuli relative to the behavioral rating, a negative s+ value was used instead of "1" to designate a Good Disk presentation. Similarly, to assess increased and decreased activation to negative stimuli, the final two analyses utilized an individual's s- rating in a place of a "1" in the design file to designate a Bad Disk presentation. One analysis used a positive s- value to assess for increased activation while the other analysis used a negative s- value to assess for decreased activation. Square waveforms were generated to represent the timing of stimuli presentations.

The fMRI scan measures the blood-oxygen-level-dependent (BOLD) signal for different brain regions and approximates brain activation by locating where oxygen is being sent in the brain based on oxygenation changes. The oxygenation change following brain activity is a hemodynamic response in which the blood oxygenation levels initially "dip" before increasing to a level that overcompensates this dip (Devlin, 2017). To account for this hemodynamic response, the double gamma function contains both

positive and negative functions to account for the timing of the increase and decrease in oxygen during he BOLD signal. Therefore, the square waveforms representing the timing of stimuli presentations were converted to double gamma hemodynamic response functions using FILM (FMRIB's Improved Linear Model) to estimate the hemodynamic response parameters of each explanatory variable versus the fixation point.

EPI scans (fMRI) were spatially normalized to each subject's anatomical image and the ICBM152 T1 template using the FLIRT module (FMRIB's Linear Image Registration Tool). The effect and standard error for all images were pooled using a fixed effects model to create a single set of statistical images for each subject. A level 1 analysis using FLAME 1 module (FMRIB's Local Analysis of Mixed Effects) pooled statistical maps across each subject group. To combine images by group association, a level 2 analysis generated an F-map produced on a voxel-by-voxel basis of parameter estimates. These parameter estimates allowed for comparisons between groups.

MRI analysis included the examination of nine *a priori* regions of interest (ROI). Primary *a priori* regions included the nucleus accumbens (NAc), amygdala, and substantia nigra/ventral tegmentum (SN/VTA). Secondary hypotheses examined activation within the orbital frontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), caudate, hypothalamus, insula, and anterior cingulate cortex (ACC). While the primary regions have well-documented involvement in loss aversion, the secondary *a priori* regions were included an exploratory analyses using regions that have documented involvement in reward processing but do not yet have a strong association with behavioral loss aversion. Six of the ROI masks were segmented using the Harvard-Oxford cortical and subcortical atlas spatially normalized to the ICBM152 template for

each hemisphere. The masks of the SN/VTA, DLPFC, and hypothalamus was segmented by an anatomist using a landmark-based, atlas-guided definition of the area (Blood et al., 2010). To reduce the number of comparisons and protect against an increased false positive rate caused by multiple comparisons, the mask for each region was bilateral (i.e., combined across hemispheres, for example, right and left insula masks were combined into one mask of the insula). Masks were overlaid onto statistical maps to localize regions meetings significance and cluster thresholds. Specifically, ROI masks generated from the Harvard-Oxford Atlases were limited to those containing 50% or higher probability of being part of the specified brain region using a probabilistic atlas. A cluster-wise Z threshold of 2.3 was used (Blood et al., 2010). The significance of each cluster was determined using FSL's cluster tool.

Neural differential sensitivity (NDS) was assessed by extracting the beta values from the Level 2 analyses using FSL Featquery. This analysis was conducted within hemispheres of regions that demonstrated the potential for significant variances in activation between Bad Disk and Good Disk presentations based on the results of the ROI analyses. Mean beta values from the Level 2 analyses were extracted from both an analysis of s- and an analysis of s+. For each subject, the beta value of s+ was subtracted from the beta value of s- and multiplied by -1 to obtain the NDS value. NDS was then correlated with the LA ratio variable to generate a Spearman's correlation coefficient. Correlations between regions were also compared following a Bonferroni correction (.05/6 = .0083).

It was predicted that:

1) When examining behavioral LA, the MDD group will exhibit greater loss aversion compared to controls.
    a) The MDD group will be more loss averse compared to controls.
    b) The MDD group will undervalue potential gains compared to controls.
2) When examining neural LA, similar neural networks will be involved for both the CON and MDD group but with different levels of hyper- and hypo-activation within these regions.
    a) The CON group will show greater activation in regions associated with higher order processing (e.g., OFC and DLPFC).
    b) The MDD group will have more activation in subcortical regions (e.g., SN/VTA, NAc, and amygdala).
3) When investigating the relationship between NDS and behavioral LA, the CON group will show a correlation between NDS in areas involved in reward neural circuitry and behavioral LA, but this relationship will not exist in the MDD group.

Participant Characteristics

A Pearson's Chi-squared test determined there was no significant difference in the distribution of participants with atypical patterns of behavioral LA between CON-FC and MDD-FC groups $X(3) = .977$, $p = .807$. Demographic variables were compared between the groups of typical LA (CON-TLA and MDD-TLA) to participants from the full cohorts (CON-FC or MDD-FC, respectively) not included in these smaller cohorts. There were no significant differences in demographic variables between the CON-TLA group and the participants from the CON-FC group not included in the final analytic sample (N=13). There was also no significant difference between the MDD-TLA group (N=20) and those from the MDD-FC group not included (N=9) in depression severity, as measured by the HAM-D, and four of the five demographic variables. However, the MDD-TLA group was less racially diverse ($X^2(3) = 10.3$, p=0.016) than those not included in the final analytic sample (see Table 1).

Table 1.

Characteristics of Individuals Not Exhibiting Typical Loss Aversion

Full Sample	CON (N=45)	MDD (N=29)
Univalent in negative direction		
N (%)	5 (11)	4 (14)
s-: M (SD)	.25 (1.19)	1.32 (.75)
s+: M (SD)	-.03 (.52)	-.47 (.27)
LA ratio: M (SD)	3.21 (3.01)	5.17 (6.22)
Univalent in positive direction		
N (%)	6 (13)	5 (17)
s-: M (SD)	-1.40 (.89)	-1.63 (1.53)
s+: M (SD)	.92 (.30)	.73 (.26)
LA ratio M (SD)	1.48 (.72)	2.69 (3.52)
Bivalent in opposite direction than expected		
N (%)	1 (2)	0
s-	-.50	
s+	-7.30	
LA ratio	6.86	

Demographic information for both samples is included in Table 2. In both the CON-TLA and MDD-TLA groups, the analytic sample was evenly distributed by sex (50-55% female, respectively), predominantly white (81-100%), post-high school educated (16.1 & 15.5 years), and primarily right-handed (88-90%). Mean age was 34.5 years (SD =9.9) in the CON-TLA group and 39 years (SD = 11.2) in the MDD group. The mean depression severity score in the MDD-TLA group was 22.8 (SD = 7.8), falling in the 'Severe Depression' range (Hamilton, 1967).

Table 2.

Participant Demographics

	Full Sample (N=74)		Typical LA (N=52)	
	CON-FC (N=45)	MDD-FC (N=29)	CON-TLA (N=32)	MDD-TLA (N=20)
Female: N (%)	23 (51)	15 (52)	16 (50)	11 (55)
Age: M (SD)	35.5 (9.8)	37.7 (10.8)	34.5 (9.9)	39 (11.2)
Race: N (%)				
White	34 (76)	25 (86)	26 (81)	20 (100)
Black	6 (13)	2 (7)	3 (9)	0 (0)
Asian	3 (7)	0 (0)	2 (6)	0 (0)
American Indian	2 (4)	1 (3)	1 (3)	0 (0)
Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Mix	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	1 (3)	0 (0)	0 (0)
Yrs of Education: M (SD)	15.9 (2.6)	15.5 (2.4)	16.1 (2.7)	15.5 (2.6)
Right Handed: N (%)	39 (87)	27 (93)	28 (88)	18 (90)
Depression severity: M (SD)	-	22.8 (7.9)	-	22.8 (7.8)

Note. Handedness determined by Edinburgh Handedness Scale; Depression severity measured by Hamilton Rating Scale – Depression (HAM-D)

Behavioral Results

Behavioral LA results are found in Table 3. In both the CON-FC and MDD-FC cohorts, none of the LA variables (i.e., s-, s+, and LA ratio) were assessed to be normal by the Shapiro-Wilk's test. Grubb's test was used to identify extreme outliers. For s-, one

MDD-FC participant was identified as an outlier and was removed from the behavioral analyses. For s+, one CON-FC participant was identified as an outlier and removed. For LA ratio, one CON-FC and two MDD-FC participants were identified as outliers and were removed. Following the removal of outliers, all three LA variables continued to fail normality tests (s-: CON p=.000, MDD p=.014; s+: CON p=.012, MDD p=.025; LA ratio: CON p=.000, MDD p=.003). Therefore non-parametric tests (i.e., Mann-Whitney) were used to compare CON-FC and MDD-FC groups.

Results demonstrated s- in the MDD-FC group did not differ significantly from the CON-FC group (U = 582.00, z = -.545, p = .295). However, s+ showed a trend towards being higher in the CON-FC group (U = 471.00, z = -1.883, p = 0.03), indicating a greater approach in the CON-FC group to positive stimuli than the MDD-FC group. There also was no difference for the LA ratio between the CON-FC and MDD-FC groups (U = 556.500, z = -.444, p = .331).

In the CON-TLA and MDD-TLA groups, the s- and s+ variables were assessed to be normal by Shapiro-Wilk's test ($p \geq .064$). Therefore, an independent samples t-test (1-tailed) was used to compare s- and s+ between groups. The LA ratio values were not normally distributed for both the CON-TLA and MDD-TLA cohorts. Outliers were identified using the Grubb's test, and one outlier from each cohort was detected and removed. The LA ratio variable was not normally distributed following the removal of the extreme outliers. Therefore, a Mann-Whitney Test was used to compare the LA ratio between groups. These participants with LA ratio outliers were not removed from the imaging analyses because those analyses utilized only the s- and s+ variables.

Results demonstrated no significant difference in s- slopes between the CON-TLA and MDD-TLA groups [$t((50) = .158$, $p > .05$]. However, during Good Disk presentations, there was a trend that indicated the CON-TLA group had higher s+ slopes compared to the MDD group [$t(50) = 1.817$, $p = .0375$}. The LA ratio did not differ significantly between the CON-TLA and MDD-TLA groups ($U = 239.500$, z = -1.099, $p = 1.38$).

Table 3.

Behavioral Loss Aversion Characteristics by Group

Groups	Full Cohort				Analytic Sample with typical loss aversion			
	CON-FC		MDD-FC		CON-TLA		MDD-TLA	
Variables	N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)
s-	45	.79 (1.17)	28	.95 (1.04)	32	1.30 (.56)	20	1.27 (.67)
s+	44	.58 (.38)	29	.41 (.44)	32	.63 (.25)	20	.50 (.24)
LA ratio	44	2.42 (1.73)	27	2.58 (1.98)	31	2.16 (1.07)	19	2.63 (1.64)

Neuroimaging Results

ROI Analyses for CON-TLA and CON-MDD.

When the positive s- variables were used as regressors, only the CON-TLA group showed increased activation in the primary *a priori* regions, specifically, the R/L SN/VTA (See Table 4). However, several secondary *a priori* regions showed increased activation in both groups, including the R/L DLPFC, R/L OFC, and the R Insula. Other secondary regions were only activated in the CON-TLA group, specifically the R/L Caudate, R/L Hypothalamus, L ACC, and L Insula. Although results from both group means had regions with significant clusters, these clusters did not remain significant when the two groups were compared.

Table 4.

ROI Results for Analysis of Positive s- Regressors to Bad Disk Presentation

ROI	Group	Hemi	Voxels	Peak Z	*p* Value	Peak Coordinates (mm) x	y	z
Primary Regions								
Amygdala	CON-TLA							
	MDD-TLA							
NAc	CON-TLA							
	MDD-TLA							
SN/VTA	CON-TLA	R/L	77	5.15	.00496	-10	-16	-14
	MDD-TLA							
Secondary Regions								
Insula	CON-TLA	R	185	4.57	.00804	34	22	-22
		L	192	5.58	.00732	-40	16	-2
	MDD-TLA	R	95	4.43	.0304	36	18	0
Caudate	CON-TLA	R	67	3.98	.0416	14	6	12
		L	149	4.6	.0111	-14	2	14
	MDD-TLA							
DLPFC	CON-TLA	R	766	4.17	.00013	46	30	36
		R	323	4.96	.00895	26	-8	54
		L	1943	5.26	5.96e-8	-24	-8	48
	MDD-TLA	R	1675	5.47	1.79e-7	44	38	28
		L	1836	5.6	5.96e-8	-24	2	54
Hypo	CON-TLA	R	14	4.44	.0447	10	-10	-8
		L	49	4.48	.0189	-8	-10	-4
	MDD-TLA							
ACC	CON-TLA	L	110	4.26	.028	-4	28	28
	MDD-TLA							
OFC	CON-TLA	R	203	5.9	.00866	34	24	-12
		L	339	5.16	.00171	-32	22	-10
	MDD-TLA	R	122	4.08	.027	42	22	-8
		L	122	4.12	.027	-30	28	-2

Note: Region of interest analyses utilizing positive s- variables unique to each individual as regressors when the Bad Disk was presented resulted in increased activation in several regions. Both the CON-TLA and MDD-TLA groups demonstrated increased activation in all secondary regions hypothesized, but only the CON-TLA group demonstrated significant increased activation in the SN.VTA to the Bad Disk. NAc = Nucleus Accumbens; SN/VTA = substantia nigra/ventral tegmentum area; DLPFC = dorsolateral prefrontal cortex; Hypo = Hypothalamus; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex

Results from the analyses that utilized negative s- variables as regressors suggested some areas of decreased activation in response to the Bad Disk presentation for both groups (See Table 5). In the primary regions, CON-TLA and MDD-TLA groups

showed decreased activation in the R NAc, but only MDD-TLA showed decreased activation in the L NAc. In the secondary regions, the L Insula and R OFC reached significance in both groups. The MDD-TLA group also showed decreased activation in the R ACC. The contrast between groups yielded no significant results.

Table 5.

ROI Results for Analysis of Negative s- Regressors to Bad Disk Presentation

ROI	Group	Hemi	Voxels	Peak Z	*p* Value	Peak Coordinates (mm) x	y	z
Primary Regions								
Amygdala	CON-TLA							
	MDD-TLA							
NAc	CON-TLA	R	14	3.31	.0202	8	18	-4
	MDD-TLA	R	24	3.76	0.151	6	12	-6
		L	7	2.78	.0258	-6	8	-8
SN/VTA	CON-TLA							
	MDD-TLA							
Secondary Regions								
Insula	CON-TLA	L	74	4.22	.0437	-38	-16	2
	MDD-TLA	L	120	4.52	.0204	-36	-20	6
Caudate	CON-TLA							
	MDD-TLA							
DLPFC	CON-TLA							
	MDD-TLA							
Hypo	CON-TLA							
	MDD-TLA							
ACC	CON-TLA							
	MDD-TLA	R	85	3.52	.0422	2	38	4
OFC	CON-TLA	R	145	4.5	.0192	24	30	-16
	MDD-TLA	R	125	3.61	.0258	32	30	-16

Note: Region of interest analyses utilizing negative s- variables unique to each individual as regressors when the Bad Disk was presented resulted in decreased activation in the right NAc, righ OFC, and left Insula for both CON-TLA and MDD-TLA. The MDD-TLA group also had decreased activation in the right ACC and left. No contrasts between groups reached significance. NAc = Nucleus Accumbens; SN/VTA = Substantia Nigra/Ventral Tegmentum Area; DLPFC = Dorsolateral Prefrontal Cortex; Hypo = Hypothalamus; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex

In the analysis of positive s+ as a regressor, results indicate several regions with increased activation to the Good Disk presentation; however, none of the primary regions reached significance (see Table 6). In the secondary regions, the R Insula, R/L DLPFC, R/L ACC, and R/L OFC showed increased activation to the Good Disk in both groups.

Only the CON-TLA group had increased activation in the L Insula and R Hypothalamus37

No group contrasts reached significance.

Table 6.

ROI Results for Analysis of Positive s+ Regressors to Good Disk Presentation

ROI	Group	Hemi	Voxels	Peak Z	*p* Value	Peak Coordinates (mm) x	Y	z
Primary Regions								
Amygdala	CON-TLA							
	MDD-TLA							
NAc	CON-TLA							
	MDD-TLA							
SN/VTA	CON-TLA							
	MDD-TLA							
Secondary Regions								
Insula	CON-TLA	R	214	5.33	.00447	34	22	-4
		L	210	5.28	.00473	-32	22	-4
	MDD-TLA	R	104	4.18	.0242	34	20	2
Caudate	CON-TLA	L	191	4.39	.00516	-12	4	10
	MDD-TLA							
DLPFC	CON-TLA	R	1861	5.97	1.58e-8	28	-6	48
		L	2252	5.75	1.23e-9	-40	4	26
	MDD-TLA	L	1848	4.93	1.72e-8	-42	34	34
		R	1714	5.42	5.96e-8	46	28	32
Hypo	CON-TLA	R	46	4.02	.0201	10	-10	-10
	MDD-TLA							
ACC	CON-TLA	R	132	5.13	.0177	4	10	42
		L	164	5.7	.0108	-2	26	30
	MDD-TLA	R	144	3.92	.0239	2	12	40
		L	85	3.76	.0398	-4	20	34
OFC	CON-TLA	R	201	5.47	.00733	34	24	-6
		L	296	5.12	.0021	-32	22	-8
	MDD-TLA	R	160	3.58	.0133	36	22	-8
		L	124	3.78	.0235	-32	22	-8

Note: Region of interest analyses utilizing positive s+ variables unique to each individual as regressors when the Good Disk was presented resulted in decreased activation in all secondary regions. Deactivation was seen in both CON-TLA and MDD-TLA groups with the exception of the left Caudate and right Hypothalamus that were deactivated in CON-TLA only. No contrasts between groups reached significance. NAc = Nucleus Accumbens; SN/VTA = substantia nigra/ventral tegmentum area; DLPFC = dorsolateral prefrontal cortex; Hypo = Hypothalamus; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex

In the fourth and final ROI analysis, negative s+ values were used as regressors during the Good Disk presentation. In the primary regions, only the NAc in the CON-TLA showed decreased activation to the Good Disk presentation (See Figure 3). In the secondary regions, both groups showed decreased activation in the L Insula and R ACC, and the CON-TLA group also showed decreased activation in the R OFC (See Table 7). No group contrasts reached significance.

Deactivation in NAc in CON-TLA in Response to Bad and Good Disk Presentations

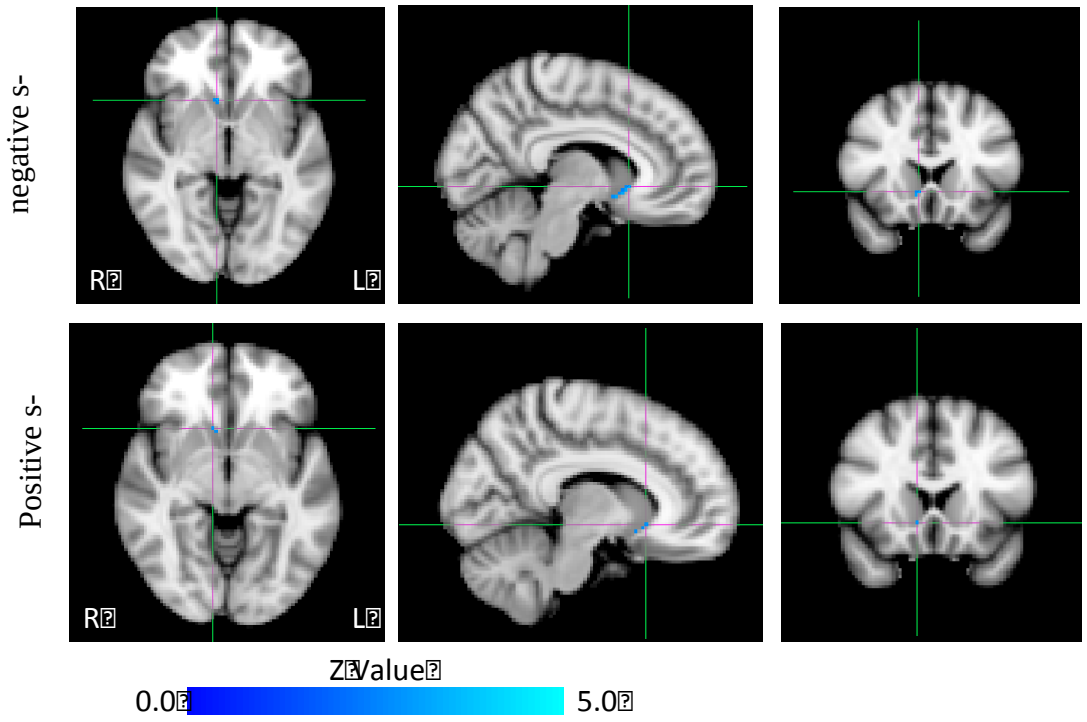

Figure 3. In the CON-LA group, right Nucleus Accumbens (NAc) had decreased activation to both Bad Disk and Good Disk presentations. This crosshairs indicate the location of the peak voxel within each significant cluster of the NAc. The MDD-LA group demonstrated decreased activation in the right NAc to the Bad Disk but not Good Disk presentation.

Table 7.

ROI Results for Analysis of Negative s+ Regressors to Good Disk Presentation

ROI	Group	Hemi	Voxels	Peak Z	*p* Value	Peak Coordinates (mm) x	y	z
Primary Regions								
Amygdala	CON-TLA							
	MDD-TLA							
NAc	CON-TLA	R	6	2.74	.0291	10	18	-6
	MDD-TLA							
SN/VTA	CON-TLA							
	MDD-TLA							
Secondary Regions								
Insula	CON-TLA	L	83	4.63	.0353	-38	-16	14
	MDD-TLA	L	69	3.98	.0461	-36	-20	6
Caudate	CON-TLA							
	MDD-TLA							
DLPFC	CON-TLA							
	MDD-TLA							
Hypo	CON-TLA							
	MDD-TLA							
ACC	CON-TLA	R	103	5.54	.0288	4	36	-6
	MDD-TLA	R	74	3.15	.0489	4	40	-4
OFC	CON-TLA	R	90	4.31	.0422	12	28	-20
	MDD-TLA							

Note: Region of interest analyses utilizing negative s+ variables unique to each individual as regressors when the Good Disk was presented resulted in decreased activation in the Right Insula and R ACC for both CON-TLA and MDD-TLA. The CON-TLA group also had decreased activation in the Right NAc and OFC. No contrasts between groups reached significance. NAc = Nucleus Accumbens; SN/VTA = substantia nigra/ventral tegmentum area; DLPFC = dorsolateral prefrontal cortex; Hypo = Hypothalamus; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex

Comparison of Neural Differential Sensitivity.

Results of ROI analyses highlighted four regions for further NDS investigation: R NAc, L Insula, R ACC, and R OFC. These regions were chosen for further analysis because they showed difference in activation across conditions, and in particular, differences in decreases in activation across Good Disk and Bad Disk presentations. Participants whose LA ratio variables were determined to be extreme outliers and were excluded from the behavioral analyses were also excluded from these analyses. Therefore,

these analyses consisted of 31 CON-TLA and 19 MDD-TLA. In the CON-TLA group, 40 there was a positive correlation using Spearman's rank correlation between NDS in the R OFC and the LA ratio, which was statistically significant (r_s = .451, *p* (one-tailed) = .005) (See Figures 4-5). No significant correlations were shown in the R NAc, L Insula, or R ACC in the CON-TLA group (See Table 8). Results yielded non-significant correlations between NDS and behavioral LA in the MDD-TLA group (Table 9).

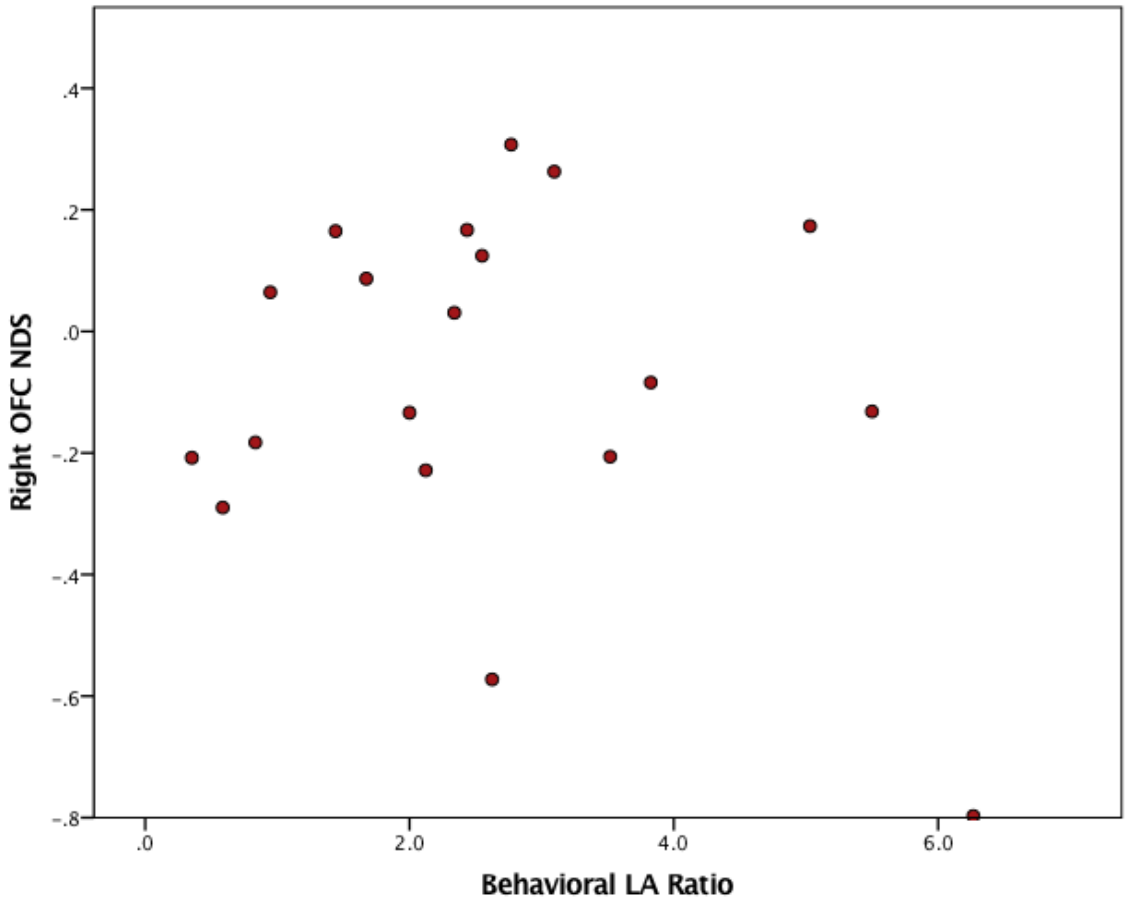

Figure 4. This graph demonstrates the correlation within the CON-TLA group between behavioral LA ratio and Neural Differential Sensitivity (NDS) in Orbital Frontal Cortex (OFC). NDS in the right hemisphere of the OFC was significantly correlated with the behavioral LA ratio.

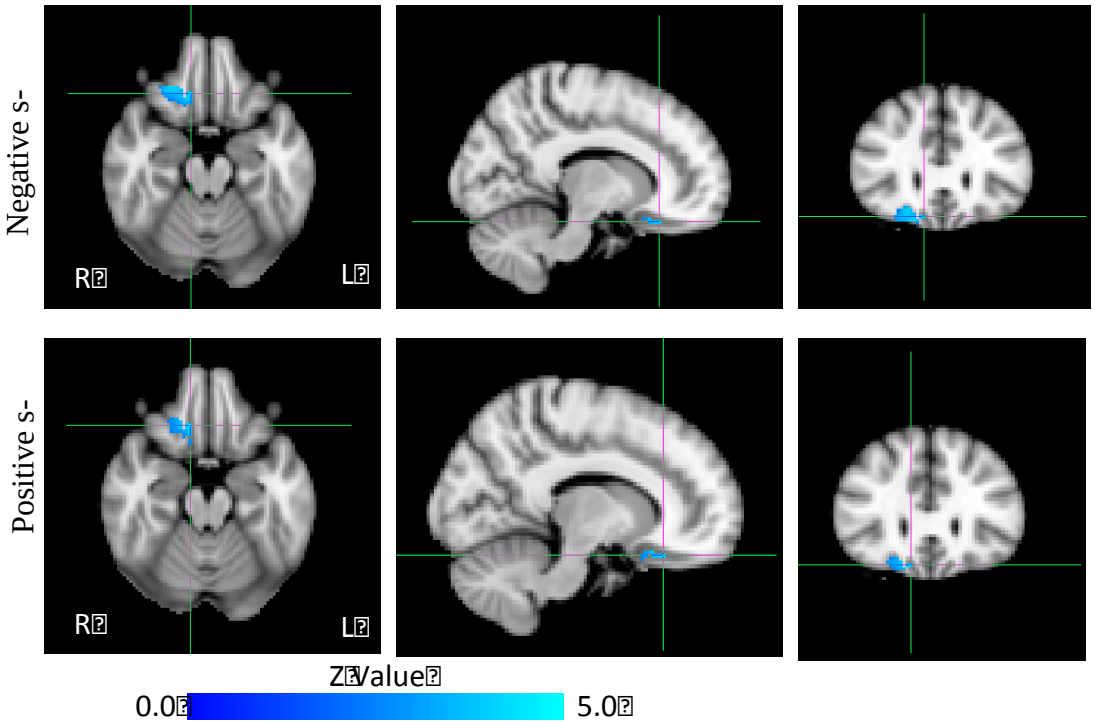

Figure 5. In the CON-LA group, right Orbital Frontal Cortex (OFC) had decreased activation to both Bad Disk and Good Disk presentations. This crosshairs indicate the location of the peak voxel within each significant cluster of the OFC.

Table 8.

Correlations Between Behavioral Loss Aversion and Neural Differential Sensitivity in CON-TLA Group

Variables		LA ratio	Right NAc NDS	Left Insula NDS	Right ACC NDS	Right OFC NDS
LA ratio	Correlation Coefficient	1.000	-.017	.066	.200	.451**
	Sig. (1-tailed)	.	.465	.362	.141	.005
	N	32	31	31	31	31
Right NAc	Correlation Coefficient	-.017	1.000	**.467****	**.496****	**.637****
NDS	Sig. (1-tailed)	.465	.	.004	.002	.000
	N	31	31	31	31	31
Left Insula	Correlation Coefficient	.066	**.467****	1.000	**.810****	.282
NDS	Sig. (1-tailed)	.362	.004	.	.000	.062
	N	31	31	31	31	31
Right ACC	Correlation Coefficient	.200	**.496****	**.810****	1.000	**.450****
NDS	Sig. (1-tailed)	.141	.002	.000	.	.006
	N	31	31	31	31	31
Right OFC	Correlation Coefficient	.451**	**.637****	.282	**.450****	1.000
NDS	Sig. (1-tailed)	.005	.000	.062	.006	.
	N	31	31	31	31	31

Note: For the NDS analyses, the mean beta values for each region were extracted from the negative s- analyses and negative s+ analyses. NDS is defined as the beta of s- minus the beta of s+. Spearman's correlation coefficient was calculated between behavioral loss aversion ratio and NDS. NDS = Neural Differential Sensitivity; NAc = Nucleus Accumbens; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex. **Bolded** coefficients indicate the correlation between regions is significant following the Bonferroni correction for multiple comparisons (.05/6 = .0083).

**. $p <$ 0.01 level (1-tailed).

Table 9.

Correlations Between Behavioral Loss Aversion and Neural Differential Sensitivity in MDD-TLA Group

Variables		LA ratio	Right NAc NDS	Left Insula NDS	Right ACC NDS	Right OFC NDS
LA ratio	Correlation Coefficient	1.000	.047	.142	-.137	.135
	Sig. (1-tailed)	.	.424	.281	.288	.291
	N	20	19	19	19	19
Right NAc	Correlation Coefficient	.047	1.000	.432*	**.739****	**.807****
NDS	Sig. (1-tailed)	.424	.	.033	.000	.000
	N	19	19	19	19	19
Left Insula	Correlation Coefficient	.142	.432*	1.000	.530**	.249
NDS	Sig. (1-tailed)	.281	.033	.	.010	.152
	N	19	19	19	19	19
Right ACC	Correlation Coefficient	-.137	**.739****	.530**	1.000	**.635****
NDS	Sig. (1-tailed)	.288	.000	.010	.	.002
	N	19	19	19	19	19
Right OFC	Correlation Coefficient	.135	**.807****	.249	**.635****	1.000
NDS	Sig. (1-tailed)	.291	.000	.152	.002	.
	N	19	19	19	19	19

Note: For the NDS analyses, the mean beta values for each region were extracted from the negative s- analyses and negative s+ analyses. NDS is defined as the beta of s- minus the beta of s+. Spearman's correlation coefficient was calculated between behavioral loss aversion ratio and NDS. NDS = Neural Differential Sensitivity; NAc = Nucleus Accumbens; ACC = Anterior Cingulate Cortex; OFC = Orbital Frontal Cortex. **Bolded** coefficients indicate the correlation between regions is significant following the Bonferroni correction for multiple comparisons (.05/6 = .0083).

*. $p <$ 0.05 level (1-tailed).

**. $p <$ 0.01 level (1-tailed).

Correlations between regions examined for NDS resulted in several significant correlations between regions. In the CON-TLA group, all four regions were significantly correlated following corrections for multiple comparisons with the exception of the R OFC and L Insula association, which was at a trend level. In the MDD-TLA group, only the R NAc, R ACC, and R OFC were correlated below the corrected $p < .0083$ value.

These correlations were also stronger ($r_s \geq .635$) in the MDD-TLA than the CON-TLA group although they were not significantly different when compared using Fisher's r to z transformation (two-tailed). Trends existed between the L Insula and both the R NAc and R ACC (see Figure 6).

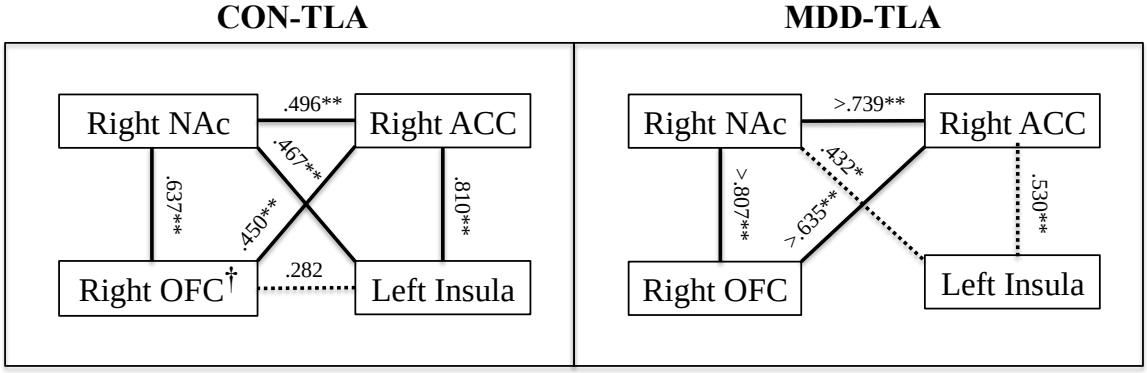

Figure 6. Spearman's rho correlation coefficients are shown between regions examined for Neural Differential Sensitivity (NDS) for each group. Solid lines indicate significant correlations following Bonferroni correction ($p < .0083$). Dotted lines indicate correlations that represent trends ($p < .1$) toward significance.
*. $p < 0.05$ level (1-tailed).
**. $p < 0.01$ level (1-tailed).
> Correlations are stronger in the MDD-TLA group than in the CON-TLA group.
† NDS of this region is also significantly correlated with LA ratio.

In this study, we explored the differences in LA between groups of depressed and healthy individuals in three ways: behaviorally, neurologically, and through correlations of behavioral and neural LA. For Aim 1, the CON-TLA group trended towards higher evaluation of potential rewards than the MDD-TLA group. Results of Aim 2 showed that both healthy controls and depressed patients showed similar patterns of neural activation relative to subjective ratings of losses and gains, but the CON-TLA group showed neural activation in more regions than the MDD-TLA group. Specifically, in the *a priori* regions, the CON-TLA group had decreased activation in the R NAc to both positive and negative stimuli whereas the depressed group had decreased activation in the R and L NAc to only negative stimuli. The CON-TLA group also showed increased activation to potential losses in the SN/VTA. Results of Aim 3 showed an association between behavioral LA and NDS for the CON-TLA group in the R OFC but not for the MDD-TLA group.

Behaviorally, we expected the depressed group to exhibit increased LA compared to controls. Results found no differences in the LA ratio (i.e., absolute value of s-/s+) between the MDD-TLA and CON-TLA groups. However, further inspection of the individual slopes of s- and s+ showed that the CON-TLA group exhibited a trend towards a higher s+ slope. This suggests that the two groups may demonstrate differences in behavioral LA, but the difference was specific to a decreased evaluation of potential gains for depressed patients compared to controls.

These findings are inconsistent with other studies that have found behavioral differences in the LA ratio (Pammi et al., 2015; Smoski et al., 2008). Still, the actual answer may be more complicated. Within our sample, we excluded depressed patients

with co-morbidities, including anxiety. This may have created a more homogeneous sample that those used in other studies. Also, research has shown that even within depressed populations, other factors beyond MDD diagnosis, such as experience of childhood trauma, affects LA patterns (Huh, Baek, Kwon, Jeong, & Chae, 2016). This raises the possibility that depression alone is not enough to significantly alter behavioral LA between depressed and control populations, and that other variables may be needed to understand the impact of experiences that may be disrupting increasing LA in depressed populations. However, even without considering these additional variables, our results suggested that that when using the greater specificity of examining s- and s+ slopes along with the LA ratio, differences may exist in reward evaluation of positive stimuli between depression and healthy subjects.

Results also showed that not all subjects exhibited typical LA. Some participants rated potentially positive outcomes as negative (i.e., univalent in the negative direction), some rated potentially negative outcomes as positive (i.e., univalent in the positive direction), and one person did both (i.e., bivalent in opposite direction). Although it did not reach statistical significance, a higher percentage of those with MDD tended to have bivalent value functions towards the negative direction compared than the healthy control group. There is a possibility that this relates to depression symptomatology and may represent meaningful subgroups within both the healthy control and depressed population. Although we were not powered for those analyses, future research should examine the symptom profiles and developmental histories of individuals with atypical LA patterns that are not typical.

Through our model-based approach, we were able to separately assess the increases and decreases in neural activation to potential losses and gains. This model-based approach also gave us the unique ability to do so using relative approach/avoidance ratings from each individual as a regressor and thus examine increases and decreases in activation based on behavioral evaluation of relative losses and gains. From these analyses, contrary to our hypotheses, only two of the three *a priori* regions showed any activation. Contrary to findings by other researchers used a forced choice paradigm (Pammi et al., 2015), there was no amygdala activation related to LA for either stimuli or for either group. The SN/VTA activation was only seen in the CON-TLA group and showed increased activation to Bad Disk. Several previous studies support the role of the VTA as an important region in motivation and reward processing (Lammel et al., 2014; Matsumoto & Hikosaka, 2009). Our findings of abnormal brain activation in the SN/VTA supports previous research using the same study cohort that showed patients with MDD had microstructural abnormalities in the SN/VTA (Blood et al., 2010). Furthermore, studies of stress-induced depression, often used to generate rodent models for depression, show that disruptions of the dopamine neurons of the VTA that project to the NAc are important for exhibiting depression-associated behaviors (Lammel et al., 2014). Our findings showed the R NAc had decreased activation to both positive and negative stimuli in CON-TLA whereas in the MDD-TLA group, the R and L NAc had decreased activation to only the negative stimuli. This raises the possibility that the potential disruption of NAc involvement in processing potentially rewarding stimuli may be the counterpose of an underactivation in an area of higher order processing in the cortex that regulates the response of the NAc in healthy individuals but not in depressed patients.

When looking at secondary *a priori* regions, as hypothesized, several regions were implicated in the processing of positive and negative stimuli in both groups, suggesting an overlap in the networks used for reward and punishment processing regardless of psychopathology. In response to the presentation of the Good Disc, results showed increased activation in the R insula, R/L DLPFC, R/L ACC, and R/L OFC and decreased activation in the R ACC and L insula in both groups. In the response to the Bad Disc, the L insula showed decreased activation in both groups along with the R OFC. The R/L DLPFC and R/L OFC as well as the R Insula showed increased activation to the Bad Disk in both groups as well. Overall, these results demonstrate high levels of cortical involvement in the processing of both losses and gains with the ACC showing specific activation to good stimuli and the insula showed a split response. Specifically, the R insula increased activation towards Good Disk and the L insula increased activation to the Bad Disk. This is consistent with previous research implicating insula involvement in reward processing, although the lack of difference between MDD-TLA and CON-TLA groups was somewhat surprising. Previous studies in MDD patients relative to controls have shown in bilateral insula activation following induction of negative affect (Fitzgerald, Laird, Maller, & Daskalakis, 2008) and a decreased activation of the R insula to monetary rewards (Zhang et al., 2013). However, these studies were not specific to LA, and our findings of increased insula activation in both groups may be specific to the relative processing of losses and gains.

Several regions showed differential activation between groups. Interestingly, these differences were specific to the direction of activation. In other words, the CON-TLA group had additional regions not significant in the MDD-TLA group that showed

increased activation, and the MDD-TLA group had additional regions that showed decreased activation. Specifically, the caudate and hypothalamus were only implicated in the CON-TLA group and showed increased activation to both good and bad disks. The ACC showed a more complex relationship between groups and stimuli. Whereas the L ACC showed increased activation to the Bad Disk in the CON-TLA group, the R ACC showed decreased activation to the Bad Disk in the MDD-TLA group. When shown negative stimuli, the MDD showed decreased activation in the R OFC. These differences in activation patterns between groups, particularly in higher-level cortical areas, support the possibility that the potential differences in primary *a priori* regions between groups, namely the NAc, may be related to a more complex relationship of hypo-and hyper-activation signaling between subcortical and cortical areas.

There were no significant results in analyses of between-group contrasts. This is likely a consequence of our model-based design. With the model-based analysis that we used, the regressors were specific to each individual, making each within group contrast more heterogeneous than if standard regressors were used (e.g., "1"). Therefore, the independent variables (i.e., individual ratings of losses and gains) were not constant across groups and therefore did not allowed us to ascertain the differences in activations through a group contrast. Instead, the mean activation of each group gave an indication of how individual regions were hyper- or hypo-activating based on relative ratings of losses and gains. This approach is likely a more powerful way to compare groups because it takes into account individual differences rather than comparing two groups on much broader conditions.

To better understand the relationship between behavioral and neural LA, we examined the correlations of LA ratios and NDS (i.e., subtraction of the beta values from decreases in activation to Bad Disk minus the betas from decreases in activation to Good Disk). Of the four regions examined (i.e., R NAc, L Insula, R ACC, and R OFC), a significant correlation was only shown in the R OFC for healthy controls. This suggests that the R OFC is involved in the behavioral manifestation of LA. Involvement of the OFC is not surprising given previous findings during reward anticipation in which the OFC showed differential activation to good and bad potential outcomes (Breiter et al., 2001) (see Figure 7). Previous research has also shown that neurons in the OFC code the presence, expectation, and relative value of rewards (Price & Drevets, 2010) thought to be related to its connections integrating multimodal stimuli. The lack of OFC involvement in NDS for depressed individuals is consistent with research that disruptions in the limbic-cortical-striato-pallido-thalamic circuit are implicated in depression (Price & Drevets, 2010). Furthermore, these findings highlight that for depressed individuals, there may exist a "mismatch" between behavior and neurological processing of rewards that is contributing to an abnormal evaluation of potential loss and gains.

Prospect Phase Time Course in Orbital Frontal Cortex

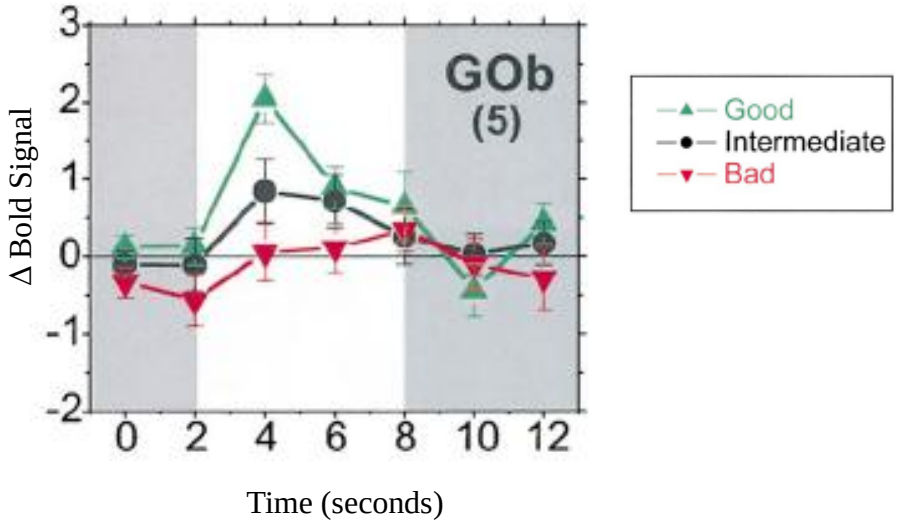

Figure 7. Time courses within the orbital gyrus (GOb) of healthy controls for good, intermediate, and bad disks show differences in BOLD activation during the expectancy phase (shown in white) of a spinner task. Activation in the GOb was strong in response to the good disk and increased monotonically with the expected value of the spinner, a response only shown in two regions (GOb and sublenticular extended amygdala). This figure used with permission (Breiter et al., 2001).

Furthermore, results suggest that the relationship between regions involved in processing rewarding and aversive information is different between depressed and nondepressed populations. While the CON-TLA group had significant correlations between all four regions involved in NDS (with a trend indicated between the L Insula and the R OFC), the MDD-TLA group did not have any significant correlations with the L Insula. Instead, the correlations between the R NAc, R OFC, and R ACC were stronger than those in the CON-TLA group, suggesting that in depressed patients, the L Insula plays less of a role while other regions may be compensating for the relative processing of potential losses and rewards.

It should be noted that we are not the first to examine LA by correlating a proxy for neural LA with behavioral ratings. Using a different paradigm for LA based based on

a different phase of expectancy (i.e., forced choice rather than anticipation of rewards and losses), Pammi and colleagues (2015) estimated neural LA by using regions that showed decreased activity for increasing loss values compared to increased activity for increasing gains (Tom et al., 2007). Their results suggested that healthy controls exhibited greater activation in the R dorsal striatum and R anterior insula whereas depressed patients showed greater activation in the VTA (Pammi et al., 2015). However, our model-based approach allowed us to use each individual's relative ratings of losses and gains as the basis for our neural LA analyses.

Research Implications

Our model-based approach for fMRI research provides important advantages over typical task-based fMRI analyses. By using behavioral data specific to each individual, we were able to make very specific predictions of how neural activation would relate to relative weighting of potential losses and gains. The importance of this type of targeted analysis of fMRI data is especially important given recent findings of the high rate of false positives in fMRI research (Eklund, Nichols, & Knutsson, 2016).

Clinical Implications

Our results suggest a trend may exist such that depressed patients undervalue potential gains compared to healthy controls. Therefore, clinicians should be mindful of this when motivating patients to engage in treatment. Patients may be less responsive to positive incentives than other patients and benefit from a "harm avoidance" approach when using motivational interviewing or discussing medication adherence. This research may also inform how clinicians conceptualize affect regulation when treating depressed individuals. Traditional psychotherapies conceptualize affect regulation as specific to

emotions without considering how reward functioning may affect these processes. Given our results that the relationship between behavioral and neural processing of rewards and losses are altered in depressed patients compared to controls, case conceptualization by treating clinicians of depressed patients may benefit from incorporating the patients' reward functioning as it may be related to emotional regulation and response to rewards and losses.

Limitations

Subjects in this study completed the Monetary Game of Chance task on one study visit. It is unclear if our findings would be stable across time. It is also unclear whether LA, as measured by this paradigm based on Prospect Theory, is influenced by depression as an emotional state versus a trait that is indicative of vulnerability to persistent depression (Brittlebank, Scott, Williams, & Ferrier, 1993). A study of LA in patients with MDD over multiple time points should be conducted to better elucidate whether the relationship between depression severity and the LA findings demonstrated in this study are related to the state of depression severity or persists across the course of either a depressive episode or following remission. Longitudinal research is also needed to understand if LA patterns in depressed patients are a consequence of depression symptomatology or a vulnerability to depression that predated the first depressive episode.

Despite the advantages of model-based fMRI compared to traditional task-based fMRI, there are some important caveats to this approach. Due to the additional constraints utilized in model-based fMRI, this may limit the ability to detect unanticipated findings (O'Doherty et al., 2007). Also, results indicate the correlation between brain region and function but cannot draw conclusions about causality

(O'Doherty et al., 2007). As with other MRI techniques, results also have poor spatiotemporal resolution (O'Doherty, Buchanan, Seymour, & Dolan, 2006). Despite these limitations, we feel that the model-based approach provided a powerful method of elucidation relationships between brain behavior and function in reward processing.

In addition, with the heterogeneous symptomatology of MDD and the variety of treatments available, within group differences may exist within our sample. For example, our sample may differ on histories of treatment (i.e., pharmacology or therapy), number of depressive episodes, current treatment, and symptoms present. Therefore, we are unable to dismiss the possibility that differences in symptom presentation and the influences of various psychiatric treatments may contribute to within group differences of the MDD group. We were also under-powered to examine possible subgroups within our heterogeneous MDD sample based on level of depression severity.

In this study, behavioral LA data was not normally distributed even following the removal of extreme outliers. This resulted in the necessity of using nonparametric tests. LA values based on ratio calculations are prone to outliers because of the way they are calculated. If the s+ value (denominator) is close to zero, the absolute ratio of LA becomes a very large number. Unfortunately, this meant that some subjects were removed from the analyses based on LA ratios that were outliers. Despite these exclusions, more conservation non-parametric tests were required that may have impacted our ability to find significant results.

Given the small number of individuals in our sample with atypical LA patterns (i.e., univalent in the positive or negative directions or bivalent in the opposite direction) we were underpowered to investigate neurological correlations of these behavior patterns.

Further research with larger samples of individuals with these LA patterns is needed to better understand if these patterns reflect subgroups of both depressed and nondepressed populations.

Future Directions

An important consideration in the area of depression neuroimaging research is that a complicating factor in understanding MDD is the phenotypic heterogeneity of the disorder. According to contemporary diagnostic criteria (DSM 5.0; American Psychiatric Association, 2013), patients must demonstrate at least 5 of 9 criteria, one of which must be either depressed mood or loss of interest or pleasure (i.e., anhedonia). Depressed patients can, as such, demonstrate a wide range of symptom patterns. For example, "it is possible for two individuals with opposing weight, appetite, sleep, psychomotor function, and mood reactivity symptoms to both fulfill a DSM-5.0 diagnosis of MDD … while only sharing a single symptom of the disorder" (Lane, 2014). Furthermore, MDD is highly comorbid with other psychiatric illnesses. Almost 43% of adults with MDD have a lifetime history that includes another psychiatric illness, and over 20% have a history of an anxiety disorder (Rohde, Lewinsohn, & Seeley, 1991). This raises the question whether MDD should continue to be viewed as a homogenous symptoms cluster with corresponding neurological abnormalities or whether subtypes exist that are reflected in both the symptomatology and neurological fingerprint of the disorder. Research has already demonstrated that subtypes of depressed patients may exist based on different levels of trait anxiety that correlates with abnormal microstructural differences in the SN/VTA (Blood et al., 2010).

Our research utilizing a unique model-based analysis of LA through an integration of behavioral and neurological substrates of depression furthers the field's understanding of depression toward a new and interdisciplinary conceptualization of mental health disorders began by the National Institute of Mental Health (NIMH). The NIMH has proposed a new classification system, the Research Domain Criteria (RDoc), that classifies psychopathology into domains based on both observable behavior and neurobiological processes (National Institute of Mental Health, n.d.). The classification incorporates several levels of analysis, including genes, molecules, behavior, and self-report and will therefore help to integrate research across disciplines to a more in-depth understanding of mental illness. The conceptualization of psychiatric illnesses into domains, in contrast to the categorical system of DSM 5.0, will help clinicians and researchers to understand and treat the high rate of comorbidity among psychiatric conditions. For example, transdiagnostic research examining reward processing abnormalities has helped to better under the neural underpinning of anhedonia, a symptom shared by three psychiatric conditions: MDD, schizophrenia, and bipolar disorder (Whitton, Treadway, & Pizzagalli, 2015). Our findings go beyond the exploration of a single symptom in depression. Our findings inform our understanding of how behaviors of LA seen in the general population may be linked to functioning of neurological circuitries that are disrupted in depression and may manifest as incongruent behavioral and neurological patterns of LA and neural compensation, but further research is needed to inform the behavioral and neural bases of impairments in psychiatric disorders.

Given the evidence that we and others have presented showing the value of using Prospect Theory to better understand psychopathology, this raises the possibility that other models of neuroeconomics that incorporate various levels of analyses, including neurological and behavioral data, can be instrumental in understanding psychopathology from a multilevel and transdiagnostic perspective like those used in RDOC. LA can also be measured behaviorally by tasks related to relative preference theory (RPT). RPT uses a mathematical formulation for LA that takes data from preference-based decision-making, but RPT does not make any parametric assumptions (Lee et al., 2015) and uses Shannon's entropy equation (Shannon, 2001) as a variable of uncertainty associated with making a choice. The advantage of this type of approach is that LA values can be used with non-monetary tasks, and research has demonstrated that LA values generated through behavioral RPT and PT tasks are correlated (Lee et al., 2015). A model of NDS derived from RPT was used to suggest that although there was no behavioral change in LA based on age, the ventral striatum/nucleus accumbens required more activation in an older population to maintain the LA behavior of younger populations (Viswanathan et al., 2015). To our knowledge, NDS of RPT has not yet been applied to psychiatric populations but has the potential to elicit disconnections between neurological and behavioral processing to provide new therapeutic targets.

Despite the pervasiveness of MDD, our treatments are still limited. Thus far, advances in our understanding of the neurological underpinnings of depression have not been translated into clinical treatment to improve patient outcomes (Blom et al., 2014). Approximately 40-60% of patients with MDD who take an antidepressant notice an improvement in their symptoms in 6-8 weeks. That is only 20% more people with

symptoms relief than if they did not take antidepressants and suggests that as many as 40-60% of patients on antidepressant experience no symptom relief (U.S. National Library of Medicine, 2017). Other interventions, such as Cognitive Behavioral Therapy (CBT), are designed to target dysfunctional cognitive biases (Disner et al., 2011). For individuals with MDD, CBT attempts to regulate distressing affective states and may also be impacting brain regions associated with emotional processing (Frewen, Dozois, & Lanius, 2008). For example, cognitive emotion regulation techniques used in CBT are designed to help patients with MDD to make more realistic appraisals of emotionally arousing situations rather then act based on the bias towards negative evaluation that is typical in MDD. Therefore, the success of CBT for MDD may be dependent on a patient's ability to utilize brain regions associated with emotional regulation (Hartley & Phelps, 2009). In fact, research suggests that greater activation in the amygdala and ACC in response to emotional stimuli in patients with PTSD predicts poorer response to CBT (Bryant et al., 2008). In MDD, increased activation in the ventromedial prefrontal cortex (VmPFC) prior to CBT predicted better treatment response, and responders also demonstrated activation changes in their amygdala and caudate following treatment (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). Using positron emission tomography (PET), researchers found insula hypometabolism was associated with depression remission following CBT and poor treatment response following pharmacotherapy (i.e., escitalopram), while insula hypermetabolism was associated with the opposite responses to treatment in each condition (McGrath et al., 2013). Research into another treatment for MDD, transcranial magnetic stimulation (TMS), found

differences in several regions, including the DLPFC, ACC, amygdala, and insula, between responders and nonresponders (Downar et al., 2014).

Our findings may provide insight into neurological underpinnings of depression symptomatology that can be targets of future treatments. Previous research provides evidence that using emotion regulation techniques similar to those in CBT can reduce LA (Sokol-Hessner et al., 2009) and reduce amygdala activation in response to loss (Sokol-Hessner et al., 2012). Given our findings that the NDS of LA was seen in controls but not in patients with depression, it leads us to wonder: If depression can be characterized as a mismatch between neurological and behavioral manifestations of LA, would CBT have an impact on LA in depressed individuals? Furthermore, would the distinctions between responder and nonresponders of CBT or other depression treatments that target reward and emotional processing circuitries be explained by an individual's NDS to LA? Further research is needed to uncover the possibility of using NDS of LA to better predict who will respond to different treatments for depressions and inform future treatment targets.

Conclusion

Taken together, comparing LA using a model-based fMRI approach resulted in both similarities and differences between individuals with and without depression. While no significant differences were found in behavioral LA between groups, our results raise the possibility that patients with MDD devalue potential gains. These results also highlight that while neural circuitries of LA may be similar between depression and healthy populations, the relationship between these regions likely differs. Depressed patients may be manifesting neural compensation with increased involvement of cortical and subcortical regions (i.e., R NAc, R ACC, and R OFC) making up the difference for

regions not involved in depressed patients (i.e., L Insula). This suggests the relationship of behavioral and neural LA using NDS and a model-based approach may hold the potential to elucidate biological substrates of depression symptomatology.

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Viswanathan, V., Sheppard, J. P., Kim, B. W., Plantz, C. L., Ying, H., Lee, M. J., … Breiter, H. C. (2017). A Quantitative Relationship between Signal Detection in Attention and Approach/Avoidance Behavior. *Frontiers in Psychology*, *8*, 122. https://doi.org/10.3389/fpsyg.2017.00122

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Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., & Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2013.06.039

EDUCATION

Clinical Psychology, Post-Doctoral Fellowship	**Harvard Medical School/ Massachusetts General Hospital**	July 2017-June 2018 (expected)
Clinical Psychology, Pre-doctoral Intern	**Harvard Medical School/ Massachusetts General Hospital**	July 2016-June 2017 (expected)
Ph.D., Clinical Psychology	**Northwestern University** Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences Dissertation: *Evaluation of Loss Aversion in Depressed Adults*	September 2011-June 2017 (expected)
M.S., Clinical Psychology	**Northwestern University** Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences Masters thesis: *Moderators and predictors of treatment response in adolescents with major depressive disorder*	September 2011-March 2014
B.A., Psychology Concentration: Biopsychology	**Boston College**	September 2003-May 2007
Study Abroad Program	**Universidad Complutense de Madrid**	January 2006-June 2006

CLINICAL TRAINING

Harvard Medical School/Massachusetts General Hospital July 2017-present
Supervisor: Alysa Doyle, PhD
Training Directors: Sheila O'Keefe, Ed.D., Ellen Braaten, Ph.D.

- **Clinical Rotations:** Learning and Emotional Assessment Program (LEAP)
- **Patient Populations:** Child & Adolescent
- **Clinical Concerns:** Mood Disorders, Anxiety Disorders, Learning Disorders, Autism Spectrum Disorders, Attention –Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Communication and Language Disorders, Complex Medical Conditions with Cognitive Deficits

- **Neuropsychological Assessment Measures:** WISC-V, WAIS-IV, WASI, WPPSI-IV, DAS-II, BEERY, Grooved Pegboard, Hooper, WCST, CPT3, DKEFS, TOWL-4, GORT-5, WJ-IV, BASC, BRIEF2, ABAS-3, WRAML 2, CVLT, ROCF, TAT, Roberts, Sentence Completion

Harvard Medical School/Massachusetts General Hospital July 2016-June 2017
Child Track; Track Director: Ellen Braaten, PhD
Training Director: Sheila O'Keefe, Ed.D

- **Clinical Rotations:** Outpatient Child & Adolescent Clinic, Learning and Assessment Program, Inpatient Adult Psychiatric Facility
- **Patient Populations:** Individual Therapy (Child & Adolescent), Family & Couples Therapy, Neuropsychological Testing (Children & Adolescents), Group Therapy (Anxiety Group, Coping Skills Group for teens with Type 1 diabetes)
- **Clinical Concerns:** Mood Disorders, Anxiety Disorders, Learning Disorders, Autism Spectrum Disorders, Attention –Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Communication and Language Disorders, Chronic Stress related to medical illness
- **Therapeutic Approach:** Cognitive Behavioral Therapy, Integrative Therapy, Parent Management Training, Couples Therapy, Family Therapy, Group Therapy

Child Study Center October 2015-May 2016
New York University Langone Medical Center
Supervisor: Richard Gallagher, Ph.D.

- **Clinical Rotations:** Outpatient Clinic, Neuropsychology Service
- **Patient Populations:** Individual Therapy (children, adolescents, & families), Neuropsychological Evaluations (Child, Adolescent, Young Adult), Group Therapy (Child Selective Mutism Group)
- **Clinical Concerns:** Attention-Deficit Hyperactivity Disorder, Selective Mutism, Learning Disorders, Anxiety Disorders
- **Therapeutic Approach:** Cognitive Behavioral Therapy, Organizational Skills Training, Parent Management Training, Classroom Observations and Intervention

University of Chicago Medical Center June 2014-June 2015
Supervisor: Tina Drossos, Ph.D.

- **Clinical Rotations:** Consult/Liaison Service for Child Psychiatry consults in Comer Children's Hospital, Health & Wellness staff in Kovler Diabetes Center, Outpatient Child and Adolescent Psychiatry Clinic
- **Patient Populations:** Individual Therapy (Child, Adolescent, & Adult), Family therapy, Group therapy (Chronic Illness Group)
- **Clinical Concerns:** Chronic Pain, pediatric hematology/oncology, head trauma, Pseudotumor, Ulcerative Colitis, Idiopathic Scoliosis, Hypothyroidism, Diabetes, Alstrom Syndrome, Gender Dysphoria, Post-traumatic Stress Disorders, Major Depressive Disorder, Fictitious Disorder, Autism Spectrum Diagnosis, Social Anxiety Disorder, Generalized Anxiety Disorder, Adjustment Disorder, Oppositional Defiant Disorder, Attention-Deficit Hyperactivity Disorder, Panic Disorder, Psychotic features, Medical Child Abuse

- **Therapeutic Approach:** Cognitive Behavioral Therapy, (Coping Cat, Treatment for Adolescents with Depression, Penn Resiliency, Trauma-Focused CBT), Parent Management Training (Incredible Years)

Ann & Robert H. Lurie Children's Hospital of Chicago July 2012-June 2014
Supervisors: Karen Gouze, Ph.D., Miller Shivers, Ph.D., & Constance Weil, Ph.D.

- **Clinical Rotations:** Outpatient Clinic, Mood and Anxiety Program, Trauma Team, Diagnostic Assessment
- **Patient Populations:** Individual Therapy (Child, Adolescent), Family Therapy, Group Therapy (Child Anxiety Group)
- **Clinical Concerns:** Post-traumatic Stress Disorder, Specific Phobia, Social Anxiety Disorder, Separation Anxiety Disorder, Generalized Anxiety Disorder, Major Depressive Disorder, Oppositional Defiant Disorder, ADHD, Obsessive Compulsive Disorder, Specific Phobia, Selective Mutism, Learning Disorder
- **Therapeutic Approach:** Cognitive Behavioral Therapy (Coping Cat, Trauma-Focused CBT), Parent Management Training (The Incredible Years, Kazdin)

Ann & Robert H. Lurie Children's Hospital of Chicago July 2012-June 2013
Supervisors: Frank Zelko, Ph.D., Jeanne Antisdel, Ph.D.

- **Clinical Rotations:** Diagnostic Assessment, Neuropsychology Service
- **Patient Populations:** Individual Diagnostic Assessment (Child, Adolescent), Group Therapy (Child Social Skills Group)
- **Diagnostic Assessment***:* Separation Anxiety Disorder, Social Anxiety Disorder, Specific Phobia, Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Adjustment Disorder, Obsessive Compulsive Disorder, Gender Dysphoria, Sexual Abuse
- **Neuropsychological Assessment:** Epilepsy, Jeavons Syndrome, Cortical Dysplasia, B12 Vitamin Deficiency, Concussion, Medulloblastoma, Astrocytoma, Pre- & Post- Surgical Evaluation, Attention-Deficit Hyperactivity Disorder
- **Neuropsychological Assessment Measures:** WISC-IV, WISC-Integrated, WAIS-IV, WASI, Boston Naming Test, Grooved Pegboard, GORT-4, WJ-III, CPT-II, BEERY, CAS, BASC, BRIEF, ABAS-II, WRAML, CMS, CVLT, WCST, Rey-Osterrieth, DKEFS, Leiter-3, BSRA-3, DAS-II, Jersilds Questions

RESEARCH

Harvard Medical School/Massachusetts General Hospital July 2017-present
PI: Kyle Williams, M.D., Ph.D.

- Evaluate neurocognitive deficits in pediatric patients with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)
- Use neuroimaging to examine neural inflammatory markers in pediatric patients with PANDAS
- Study neurological correlates of pediatric Obsessive Compulsive Disorder (OCD)

Harvard Medical School/Massachusetts General Hospital December 2016-present

PI: Anna Georgiopoulos, M.D. & Deborah Friedman, Ph.D.

- Retrospective chart review to examine the clinical experiences of adults with cystic fibrosis in the diagnosis and treatment of Attention Deficit Hyperactivity Disorder.

PI: Ellen O'Donnell, Ph.D. October 2016-present

- Evaluate the psychological and medical outcomes of a group-based treatment to develop coping skills in adolescents with Type 1 Diabetes and their caregivers

Northwestern University/Feinberg School of Medicine 06/2012-present
Warren Wright Adolescent Center

PI: Hans Breiter, M.D.

- Paradigm development for Engineering-Based Behavioral Science (EBS) projects related to quantifying behavior and neurological processing in the domains of memory, attention, and reward
- Examine reward and emotion processing in depressed adolescents and adults and explore how neurocognitive substrates of depression may have correlate to psychotherapy efficacy

Northwestern University/Feinberg School of Medicine September 2011-June 2016
Child and Adolescent Mood Laboratory

PI: Mark Reinecke, Ph.D.

- Study predictors of relapse and remission, neurocognitive substrates, and vulnerability to suicidality in adolescents with depression

Northwestern University/Feinberg School of Medicine January 2012-November 2015
Department of Medical Social Sciences

PI: Laurie Wakschlag, Ph.D. & Margaret Briggs-Gowan, Ph.D.

- Assist in the development, training, and video coding of the Family Socialization Interview (FSI) assessing conflict exposure of young children and parental discipline styles

Ann & Robert H. Lurie Children's Hospital of Chicago March 2013-June 2015

PI: Lisa Sorenson, Ph.D.

- Neuropsychological testing and scoring of intelligence, academic achievement, and sustained attention tasks

Ann & Robert H. Lurie Children's Hospital of Chicago October 2011- December 2013

PI: Jill Weissberg-Benchell, Ph.D.

- Lead cognitive behavioral group therapy based off the Penn Resiliency Program protocol to promote resiliency in adolescents with Type I diabetes

Cambridge Health Alliance/Harvard Medical School July 2010-July 2011

PI: Karlen Lyons-Ruth, Ph.D. & Martin Teicher, M.D.

- Collect and analyze imaging and cognitive data from a prospective longitudinal study examining structural and functional brain changes from early life stress

McLean Hospital/Harvard Medical School October 2010-July 2011
Child and Adolescent Mood Disorders Laboratory
PI: Randy Auerbach, Ph.D.

- Assist in the development and implementation of new research protocols, including a pilot group therapy program for adolescents with Major Depressive Disorder
- Analyze data examining gender differences in factors predicting stress and anxiety symptoms in Canadian adolescents

McLean Hospital/Harvard Medical School August 2007-June 2009
Translational Imaging Laboratory
PI: Marc Kaufman, Ph.D.

- Plan and execute studies for patient populations including nicotine dependent women, people suffering from schizophrenia, and cocaine users
- Collect and analyze neuroimaging data, including fMRI, DTI, and structural images

McLean Hospital/Harvard Medical School January 2007-June 2007
PI: Jennifer Sharpe Potter, Ph.D.

- Assist with data management of research studies conducted by the Alcohol and Drug Abuse Treatment Program

COMPETITIVE FELLOWSHIPS, HONORS, & AWARDS

2003-2007	Dean's List, Boston College
2010	Nominee, Fort Polk Volunteer of the Year
2014-2015	American Psychological Foundation (APF) Elizabeth Munsterberg Koppitz Graduate Student Fellowship ($25,000)
2014-2015	Brian Harty Fellow ($15,000)
2014	University of Michigan Training Course in fMRI, NIH-funded (PI: John Jonides, PhD)
2015	Graduate Research Grant, The Graduate School, Northwestern University ($3,000)
2015-2016	Brian Harty Fellow ($15,000)
2016-2017	P.E.O. Scholar Award ($15,000)
2016	Scholarship to Attend Health Policy Course offered by Partners Center of Expertise

TEACHING

Spring 2015 Graduate Teaching Assistant
Clin Psych 462: Cognitive therapy with children, adolescents, and families
Department of Psychiatry and Behavioral Sciences,
Northwestern University Feinberg School of Medicine; Chicago, IL

PROFESSIONAL MEMBERSHIPS/COMMITTEES

Memberships in Professional Societies*:*

2011-2016 American Psychological Association
2011-current American Psychological Association of Graduate Students (APAGS)
2011-current Association for Psychological Science (APS)
2015-current Society for a Science of Clinical Psychology (SSCP)
2016-current APA Division 53: Society of Clinical Child & Adolescent Psychology

Departmental and University Committees:

2012-2013 Student Representative to Professional Development Committee, Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences
2013-2014 Student Representative to Curriculum Committee, Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences

PUBLICATIONS

Peer-Reviewed Articles:

Janes, A.C., Frederick, B.B., **Richardt, S.,** Burbridge, C., Merlo-Pich, E., Renshaw, P.F., Evins, A.E., Fava, M., Kaufman, M.J. (2009). Brain fMRI responses to smoking-related images prior to and during extended smoking abstinence. *Experimental Clinical Psychopharmacology, 17,* 365-373.

Janes, A.C., Pizzagalli, D.A., **Richardt, S.,** Frederick, B.B., Holmes, A.J., Sousa, J., Fava, M., Evins, A.E., Kaufman, M.J. (2010). Neural substrates of attentional bias for smoking-related cues: An fMRI study. *Neuropsychopharmacology, 35,* 2339-2345.

Janes, A.C., Pizzagalli, D.A., **Richardt, S.,** Frederick, B.B., Chuzi, S., Pachas, G., Culhane, M.A., Fava, M., Evins, A.E., Kaufman, M.J. (2010). Pre-quit fMRI brain reactivity to smoking-related cues predicts future ability to maintain tobacco abstinence. *Biological Psychiatry, 67,* 722-729.

Auerbach, R.P., **Richardt, S.,** Kertz, S., & Eberhart, N.K. (2012). Cognitive vulnerability, stress generation, and anxiety: Symptom clusters and gender differences. *International Journal of Cognitive Therapy, 5*(1), 50-66.

Washburn, J.J., **Richardt, S.L.,** Styer, D.M., Gebhardt, M., Juzwin, K.R., Yourek, A. & Aldridge, D. (2012). Therapeutic approaches to non-suicidal self injury in adolescents. *Child and Adolescent Psychiatry and Mental Health, 6*(14).

O'Dor, S., Grasso, D., McCarthy, K., Forbes, D., Wakschlag, L., & Briggs-Gowan, M. (2016) The Family Socialization Interview –Revised (FSI-R): A comprehension assessment of parental disciplinary behaviors. *Prevention Science, 18*(3), 292-304.

Articles Preparation:

O'Dor, S., Washburn, J. & Reinecke, M.A. Moderators and predictors of treatment response in adolescents with major depressive disorder. *Manuscript in preparation.*

Book Chapters:

O'Dor, S. (in press). Continuous Performance Tasks. In Ellen Braaten (Ed.), *The SAGE encyclopedia of intellectual and developmental disorders*. Thousand Oaks, CA: SAGE Publications, Inc.

PEER-REVIEWED PRESENTATIONS/ABSTRACTS

Oral Presentations:

Kaufman, M.J., Janes, A.C., Udo de Haes, J., **Richardt, S.,** Olson, D., Gruber, S., Prescot, A., Schipper, J., Sjogren, M., Yurgelun-Todd, D., Renshaw, P.F. The glycine transporter (GlyT1) inhibitor Org 25935 alters default network connectivity in healthy men. [Presentation at the 2009 American College of Neuropsychopharmacology]

Janes, A.C., Frederick, B.B., **Richardt, S.,** Merlo-Pich, E., Evins, A.E., Fava, M., Renshaw, P.F., Kaufman, M.J. Pre-quit brain fMRI responses to tobacco smoking-related cues predict slips during smoking cessation treatment. [Presentation at the 2009 College on Problems of Drug Dependence]

Kaufman, M.J., Janes, A.C., Frederick, B.B., **Richardt, S.,** Burbridge, C., Merlo-Pich, E., Renshaw, P.F., Evins, A.E., Fava, M. Brain reactivity to smoking-related cues during tobacco abstinence: an fMRI study. [Presentation at 2008 American College of Neuropsychopharmacology]

Janes, A.C., Frederick, B.B., Burbridge, C., **Richardt, S.,** Evins, A.E., Fava, M., Renshaw, P.F., Kaufman, M.J. Women on Nicotine Replacement Therapy Show Significant Brain Activity in Response to Smoking Cues [Presentation at 2008 College on Problems of Drug Dependence]

Pechtel, P. & Lyons-Ruth, K., Teicher, M., & **Richardt, S.** (2011). Neurobiological effects of early childhood adversity: Results from a 20+ year prospective study. [Presented at the "Early Life Stress and Trauma" symposium at the Association for Behavioral and Cognitive Therapies Conference]

Clarke, A.H., **O'Dor, S.,** & Reinecke, M. (2013) Predictors and Moderators of Treatment Response in a Sample of Depressed, Suicidal Adolescents [Presented at the "Moving Beyond Risk Factors in the Study of Adolescent and Emerging Adult Suicidal Behavior: Role of Mediators and Moderators" symposium at the Association for Behavioral and Cognitive Therapies Conference]

O'Dor, S. (2014). The Silent Response: Anxiety, Speech, Language or Opposition? Presentation at the Multi-Disciplinary Case Conference, Ann & Robert H. Lurie Children's Hospital of Chicago, Department of Psychiatry.

O'Dor, S. (2014). Case conceptualization of child with subclinical ASD. Presentation at the Multi-Disciplinary Case Conference, University of Chicago Medical Center, Department of Psychiatry and Behavioral Neuroscience.

O'Dor, S. (2014). Managing Diabetes under the Watchful Eye of the Courts: One Family's Journey. Presentation at the Endocrinology Psycho-Social Case Conference, University of Chicago Medical Center, Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism.

O'Dor, S. (2015). Understanding and Treating Non-Adherence in Adolescents: A Multidisciplinary Approach. Presentation at the University of Chicago Grand Rounds of the Department of Medicine and Pediatrics, Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism.

O'Dor, S. (2015). Case conceptualization of adolescent with MDD and uncontrolled Type 1 Diabetes. Presentation at the Multi-Disciplinary Case Conference, University of Chicago Medical Center, Department of Psychiatry and Behavioral Neuroscience.

Posters:

Janes, A.C., Pizzagalli, D.A., **Richardt, S.,** Frederick, B.B., Chuzi, S., Pachas, G., Culhane, M.A., Fava, M., Evins, A.E., Kaufman, M.J. (2009) Insula reactivity to smoking-related cues and the emotional Stroop task predict slips in tobacco smoking abstinence. [Won the Neal Allan Mysell Award given for the best Fellow poster at the Harvard Medical School Department of Psychiatry Mysell Lecture and Research Day]

Janes, A.C., Frederick, B.B., Burbridge, C., **Richardt, S**., Evins, A.E., Fava, M., Renshaw, P.F., Kaufman, M.J. (2008). Women on Nicotine Replacement Therapy Show Significant Brain Activity in Response to Smoking Cues. [Poster Session at the American Psychological Association Annual Meeting Early Career Investigators]

O'Dor, S., Connolly, M., & Reinecke, M. (2012) Psychometric Properties of the Affective Disorders Scale in a Clinical Sample. [Poster Session at Association for Psychological Science Conference, May 2012; Northwestern Feinberg School of Medicine Department of Psychiatry & Behavioral Sciences Scholars Day, May 2012]

O'Dor, S.L., Clarke, A.H., & Reinecke, M.A. (2013) Moderators and predictors of treatment response in adolescents with major depressive disorder. [Poster Session at Northwestern Feinberg School of Medicine Department of Psychiatry & Behavioral Sciences Scholars Day, May 2013]

O'Dor, S., Clarke, A.H., & Reinecke, M. (2013) Correlates of Persisting Depressive Symptoms in Adolescents following Treatment for Major Depressive Disorder. [Poster Session at the Association for Behavioral and Cognitive Therapies Conference; Northwestern Feinberg School of Medicine Department of Psychiatry and Behavioral Sciences Scholars Day, May 2014]

O'Dor, S., Lawton, R., & Drossos, T. (2015). Easier with time?: The relationship between duration of illness and HbA1c. [Association of Psychologists in Academic Health Centers; Northwestern Feinberg School of Medicine Department of Psychiatry & Behavioral Sciences Scholars Day, May 2015]

O'Dor, S. & O'Donnell, E. (2017). Effects of ADHD Symptoms on Medical Adherence: Are Executive Functioning Deficits an Extra Hurdle for Pediatric T1Diabetics? [Poster Session at Association for Psychological Science Conference, May 2017]